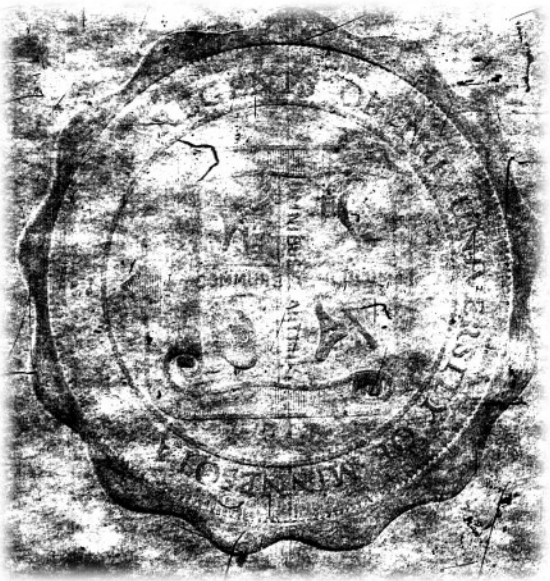

F I N A L R E P O R T

Project N 114 - 020

ELECTROLYTE BALANCE IN SURGICAL PATIENTS WITH PARTICULAR REFERENCE TO ENDOCRINE FACTORS

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TABLE OF CONTENTS

BACKGROUND

INTRODUCTION

The interest of surgeons in problems of electrolyte metabolism and parenteral therapy has developed rapidly in recent years. This interest has been stimulated to a considerable degree by the increasing magnitude of surgical procedures involving the necessity for prolonged and complicated supportive therapy and conversely, advances in the field of supportive therapy have been largely responsible for the feasibility of present-day extensive surgery. The rapid progress during the first half of this century has been made possible by the development of accurate and practicable methods by which the composition of body fluids can be assessed and on the basis of which losses can be replaced and deviations of composition restored. The outstanding contributors to the field of fluid and electrolyte balance have been pediatricians whose studies were initiated by the compelling problem of infantile diarrhea. Though until recently surgeons have been content to take over the methods which pediatricians introduced and apply them to their own specialty, it has become increasingly apparent that the surgical patient presents specific problems which deserve special consideration. This realization has resulted from the accumulation of evidence pointing to the consistent occurrence of a specific pattern of metabolic changes accompanying trauma of the degree exemplified by major surgical operations. Although the changes associated with surgical stress involve both inorganic and organic metabolism, the present dissertation will be concerned only with deviations of mineral and water balance, their possible relationship to the function of the endocrine system and the therapeutic problems which they present.

I. THE NONSPECIFIC REACTIONS OF ELECTROLYTE METABOLISM TO SURGERY

In the 1930's, French authors spoke frequently of "La Maladie Postopératoire". This syndrome which was felt to be consistently exhibited by the post-surgical patient was characterized by oliguria, with a tendency to azotemia and acidosis, hyperglycemia, increased rate of red cell sedimentation, reduction of chloride in the blood and absence of chloride in the urine (103, 106, 108, 109, 140). These

observations of consistently reduced plasma chloride levels despite small amounts of chloride in the urine of postoperative patients have been repeatedly confirmed in subsequent years (4, 6, 112, 110, 119, 124, 135, 134, 162).

The findings with regard to sodium metabolism in the postoperative patient have played a most significant role in the recent history of surgical electrolyte therapy. In 1933 Jones and Eaton under the title of "Postoperative Nutritional Edema" described the clinical edema which was common during the period when the employment of "physiological" saline solution as a hydrating fluid was widespread (100). This situation then obtained despite the fact that the dangers of saline solution had been emphasized much earlier by Trout, by Evans, and even by Dr. Matas who had been largely responsible for the introduction of continuous intravenous fluid therapy in this country (56, 116, 175). In 1945 the balance studies of Coller and his associates demonstrated the powerful tendency to retention of sodium ion by patients in the immediate postoperative period (25, 27). As a result of these experiments, it became the custom of many surgeons to administer no sodium chloride to patients on the day of surgery and during the first 24 hours following operation.

The behavior of potassium ion in the post-surgical patient has similarly received an increasing degree of attention in recent years. Cuthbertson, who through his studies of nitrogen balance had pioneered the investigation of metabolism in surgery and injury, found that in addition to nitrogen, large amounts of potassium and phosphorus were poured out in the urine of patients following fractures and operations (32, 33). The subsequent studies of Albright, Howard, Randall, Moore and many others have confirmed this and shown that the potassium-to-nitrogen ratio of the urine under these circumstances exceeds that of tissues, indicating that specific effects on potassium are concerned entirely apart from the catabolic processes involving tissue protein (12, 47, 48, 90, 123, 124, 125, 133).

Although, potassium is discharged in considerable amounts through gastrointestinal secretions, it is apparent that the major loss which leads to depletion of this ion in surgical patients is that which occurs in the urine during the postoperative period in the absence of adequate replacement therapy. Serum potassium levels are regularly seen to be lowered in postoperative patients on usual parenteral management, and the syndrome of hypokalemic alkalosis, the mechanism of which was first elucidated by Darrow in infantile diarrhea, is now recognized as a frequent complication of surgery (36, 37, 38, 39, 40, 47, 49, 51, 52, 53, 55, 114, 128, 129, 131, 133, 155).

II. HANS SELYE AND "THE GENERAL ADAPTATION SYNDROME"

Of obvious relevance to these considerations regarding nonspecific metabolic alterations in the surgical patient are the now well-known findings of Selye and his co-workers relating to the consequences of trauma in experimental animals. The concept introduced by Selye states that following the imposition of stress in animals, a series of metabolic changes occur which have the overall effect of rendering the organism more capable of surviving repeated stresses of a similar or different nature. The stages of this adaptation have been identified as follows (149, 150, 151):

(1). The Shock Phase, during which the organism is relatively decompensated with respect to the deleterious effects of the injury sustained.

(2). The Counter-Shock Phase, during which the mechanisms responsible for the development of resistance to stress are mobilized. In Selye's terminology phases (1) and (2) are together referred to as the Alarm Reaction.

(3). The Resistance Phase, in which the animal has developed resistance to further or continued trauma.

(4). The Exhaustion Phase, which represents the point at which the mechanisms of resistance break down.

Selye has brought together a vast assortment of chemical and pathological phenomena which he believes to represent processes which take place during the development of resistance to non-specific trauma. A complete discussion of these manifestations is beyond the scope of the present treatise, and one must for this consult this author's extensive reviews on the subject (145, 149, 150, 151). Of particular importance are hypertrophy of the adrenals, regression of the volume of lymphoid tissue, and reduction of lymphoid elements and eosinophilic leukocytes in the blood. The metabolic phenomena include negative nitrogen balance, increased glyconeogenisis from protein and consequent hyperglycemia and decreased glucose tolerance.

Most germaine, however, to the problem under discussion here are the modifications of mineral and water metabolism which characterize the "Adaptation Syndrome". Chloride levels of the blood were found to fall sharply during the shock phase to rise again during the countershock phase and frequently were found to be higher than normal during the phase of resistance. This pattern is illustrated in Figure 1 which is adapted from Selye's illustrations (146, 147). Sodium concentrations behave similarly. From the time of injury, however, restriction of urinary sodium and chloride excretion takes place. Potassium excretion on the contrary is found to be enhanced.

Characteristic changes in water balance have also been shown by the investigations concerned with the manifestations of stress in experimental animals. Howlett and Browne and Selye and his associates have observed pronounced tendency to water retention and to formation of edema and fluid accumulation in serous cavities during the early stages of the response to injury (19, 91, 92, 102). This occurrence is related, they believe, not only to alterations in renal function, but to changes in the permeability of capillary and other membranes.

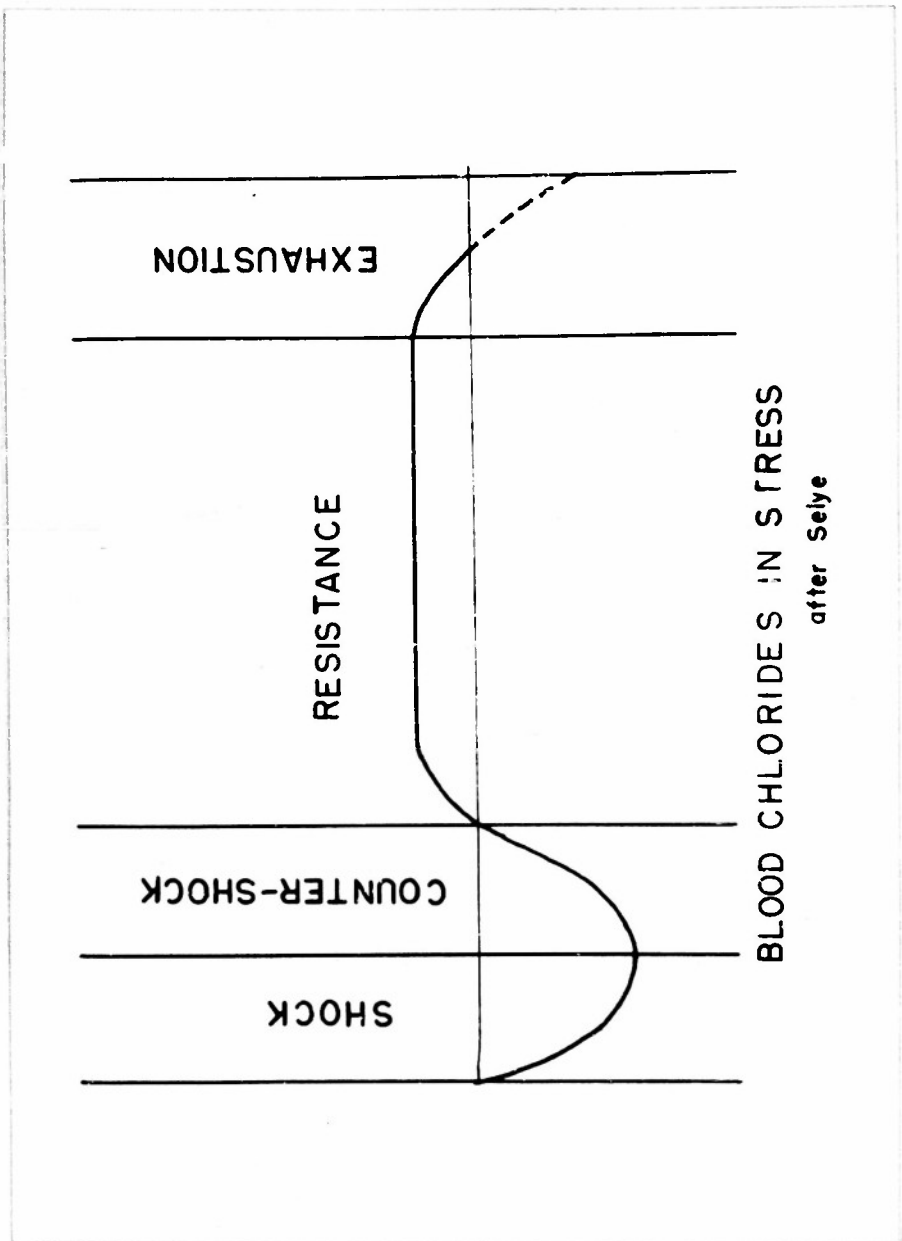


Figure 1. Course of blood chlorides following experimental stress in rats. Adapted from Selye (146).

All the adjustments which characterize the counter-shock and resistance phases are abolished by the removal of the hypophysis or the adrenal cortices. It is apparent, therefore, that these reactions are mediated by the hormones of the adrenal cortex, the secretion of which is stimulated under the circumstances of stress by the pituitary corticotrophic hormone. In the absence of the adrenals, the manifestations of the shock phase of the adaptation syndrome are more severe, more prolonged, and animals are much more likely to succumb to them. Thus it has been shown that abnormal accumulation of edema following injury is greatly increased in adrenalectomized animals. Similarly the depression of chloride levels is more profound, more prolonged, and the hyperchloremic phase less in evidence (147).

III. RECENT STUDIES RELATING METABOLIC REACTIONS IN THE SURGICAL PATIENT TO ENDOCRINE FUNCTION

That the typical changes which characterize the metabolic balance of the post-operative patient are entirely analogous to those incident to the non-specific stress response in animals is quite evident. Feyel and Varangot in 1943, studying the sodium and chloride excretion in surgical patients pointed out that this reaction was the converse of Addison's disease and postulated it was due to hyperadrenalism (57). Albright in his classic lecture on the Cushing Syndrome pointed to the parallelism between the effects of hyperadrenalism induced by that disease on the one hand and by injury and surgery on the other (2). Venning and her co-workers, and subsequently many others, demonstrated the presence of hormones of adrenal origin in the urine of patients following surgical interventions (176, 177, 178). Quantitative differences in the output of cortical steroids between healthy and chronically-ill surgical patients have also been demonstrated (50).

The development by Thorn and his co-workers of the absolute eosinophil count as a measure of adrenal function has afforded a simple method for delineating the adrenal response to operations (165). Laragh and Almy and subsequently Roche and others demonstrated that in uncomplicated surgery the eosinophil count fell

immediately and returned to normal on the 3rd to 5th postoperative day (105, 139). It is of interest in this connection that in 1907, Lams noted the absence of eosinophils in acute diseases and discussed the prognostic significance of persistent eosinopenia (104). The use of eosinopenic response to ACTH as described by Thorn and to epinephrine as introduced by Recant and her co-workers have been suggested as methods of evaluating preoperatively the patient's ability to respond to surgery (136, 165).

Recent studies have suggested a specific relationship between the postoperative alterations of fluid and mineral balance and secretion of adrenal hormones. Hardy has attached considerable significance to the fact that the duration of oliguria postoperatively runs closely parallel to the postoperative eosinopenia (75, 77, 78). He has found a similar relationship between the eosinophil level and fluid loss from gastrointestinal secretions (76). Johnson and his co-workers have demonstrated sodium-to-potassium ratio in postoparative sweat which are identical to those seen after administration of desoxycorticosterone and ACTH (99). This they have interpreted as evidence for the increased production of 11-desoxycorticosteroids after operation. The validity of such a conclusion will be subsequently discussed.

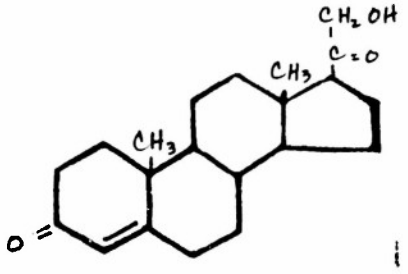
IV. THE ADRENAL HORMONES: CHEMICAL PROPERTIES

It is obviously impossible to include here an adequate discussion of the chemical nature and properties of the adrenal hormones. Our present knowledge of the chemistry of the steroid hormones is perhaps the most admirable contribution of organic chemistry in recent years and its attainment has been a complicated and arduous task. It must suffice here to present merely an outline of the major group of compounds and their best-known representatives without any detailed consideration of the investigations upon which the present concepts are based. The conventional classification of these compounds into (a) mineralocorticoids, (b) glycocorticoids and (c) androgens may eventually be disproved. Such a division nevertheless enjoys, at the present time, the benefit not only of chemical evidence, but of physiological and anatomical confirmation. It seems to be the most rational

framework upon which to consider these substances.

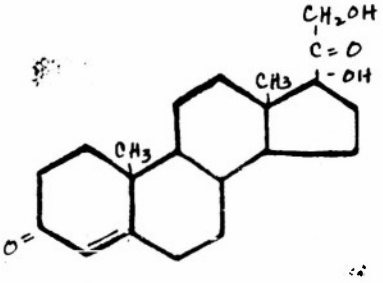
A. Eleven-desoxycorticoids. (Mineralocorticoids)

These compounds are primarily concerned with mineral exchange causing positive sodium and negative potassium balances with little or no effect on organic metabolism. The most familiar compound classified in this group of 11-desoxycorticosterone:



11-desoxycorticosterone

This substance was synthesized and Reichstein in 1937, and has been widely available commercially (156, 157). It was subsequently shown by Reichstein and von Euw to be present in beef adrenal glands, but only in extremely small amounts (12.5 mgm. per 1000 pounds of beef adrenals) (137). Although this compound replaces certain functions of the adrenal gland, being the most powerful sodium-retaining substance known, there is some doubt as to its status as a true naturally-occurring hormone. If there is an 11-desoxycorticoid which subserves the function of electrolyte regulation, it is perhaps more likely that this is 11-desoxy-17-hydroxycorticosterone (Compound S of Reichstein).

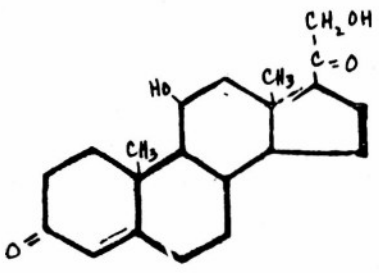


11-desoxy-17-hydroxycorticosterone

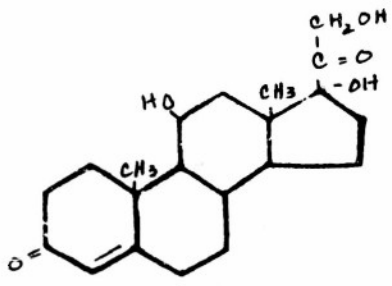
This material, though a somewhat less potent sodium retainer, has been obtained in greater amounts from adrenal glands (137, 166).

B. 11-oxycorticoids (Glycocorticoids).

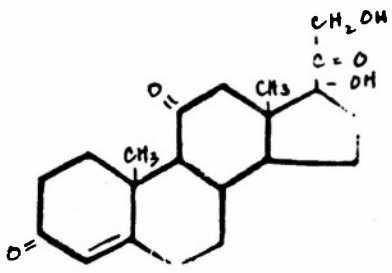
These substances are predominantly concerned with the regulation of nitrogen and carbohydrate metabolism. Chemically they differ from the first group only in the possession of either a ketone or a hydroxyl group at the 11-carbon position. The known members of this group are given below with the names by which they are usually known. (Kendall's nomenclature).



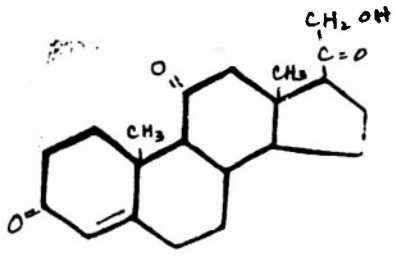
Corticosterone
Compound B



17-hydroxycorticosterone
Compound F
Hydrocortisone



17-hydroxy-11-dehydrocorticosterone
Compound E
Cortisone

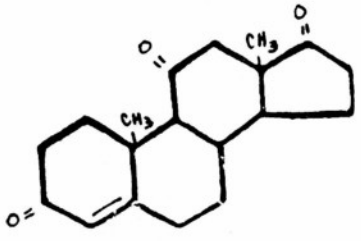


11-dehydrocorticosterone
Compound A

The most familiar of these are, of course, Kendall's Compound E and its 11-hydrogenated relative, Compound F. All of this group tend to cause negative nitrogen balance, increased glyconeogenesis from protein and decreased glucose tolerance. It is important, however, that they are not without effect on mineral metabolism. Although their effects in this regard are variable, depending on dosage, animals used, and experimental conditions, Compounds E, F, and B have all been shown under appropriate circumstances to cause positive sodium, and negative potassium balances in man (60, 164, 166, 167, 170, 171). As will be seen presently this fact may be of considerable importance when the question arises of whether specific mineral-regulating hormones need be invoked as a basis for the characteristic electrolyte propensity of the glycocorticoids is of particular significance with regard to Compound F, which some have felt to be the only important hormone produced by stress and adrenal stimulation (30, 61).

C. The Androgens

There remains a third group of adrenal steroids about whose normal function almost nothing is known. They differ from the first group in possessing only 19 instead of 21 carbon atoms. Having no side chains at the 17-carbon, they are chemically similar to the testicular androgen testosterone and presumably their function is similar. The following substance, adrenosterone is an example of such an androgen of adrenal origin.



Adrenosterone

Androgens cause positive nitrogen balance and if the adrenal androgens have a metabolic function it may be to balance the catabolic activity of the glyco-corticoids.

V. THE ADRENAL HORMONES: SOURCES; REGULATION; METABOLISM AND EXCRETION

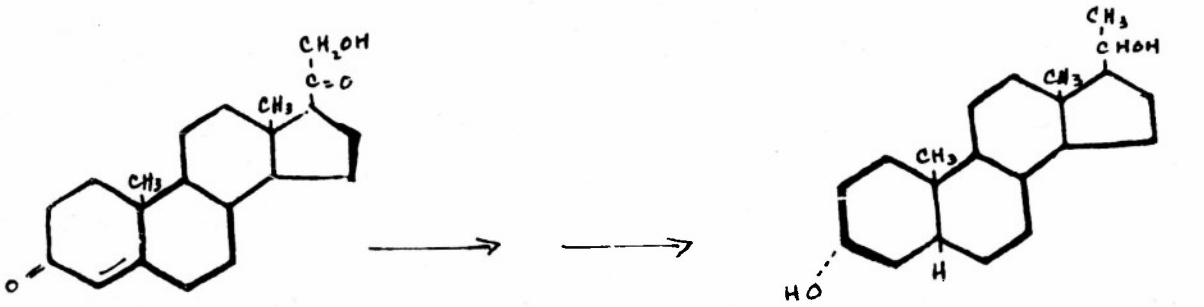
As far as is now known the secretion of glycocorticoids by the adrenal cortex is entirely under the regulation of the anterior hypophysis. At least two mechanisms appear to be involved in this regulation (111, 117, 118, 144). In the animal which is not being subjected to stress, the discharge of pituitary corticotrophic hormone was shown by Sayers to be inhibited by elevation of the blood level of adrenal steroids (22, 144). This phenomenon suggests that in the absence of stress, at least, a nice balance exists by means of which the interaction of the pituitary and the adrenals maintain a constant blood level of cortical substances. Under the circumstances of stress, however, it is probable that other mechanisms can stimulate the production of ACTH by the anterior pituitary. C.N.H. Long first showed that epinephrine was capable of stimulating corticotrophic activity (111). Advantage of this phenomenon was taken by Recant and her collaborators to develop a test for pituitary reserve (136). On the other hand more recent investigations have cast some doubt on this action of epinephrine and particularly on the validity of the "epinephrine-eosinopenia" test (128). Hume has shown that the stimulatory actions of stress are probably delivered to the anterior hypophysis by way of certain centers in the hypothalamus which he believes communicates its stimulation to the pituitary through humoral rather than neural mechanisms (94, 95, 96). Harris and associates have confirmed these findings (79, 80).

When one considers the control of electrolyte-regulating adrenal hormones the picture differs. There is no clear-cut evidence that mineralocorticoids are under the control of the anterior pituitary. The cytological studies of Greep and Deane relating to the effects of various circumstances on the character of the three cortical zones have produced some impressive information on this point (12, 42, 70, 71, 72). It was the finding of these investigators that, whereas the administration of desoxycorticosterone caused atrophy of the zona glomerulosa in rats, institution of low sodium, high potassium intakes caused enlargement of this outermost layer of cortical cells. Treatment with ACTH, on the other hand resulted

in hypertrophy which was limited to the zona fasciculata. They concluded that the zona glomerulosa was the source of mineralocorticoids and that the glycocorticoids were elaborated by the zona fasciculata. Previous observations concerning cytologic changes in certain cases of adrenal virilism had already suggested that the zona reticularis gave rise to the adrenal androgens (14). Greep and his associates further concluded that the zona glomerulosa is independent of pituitary trophic influence, being responsive only to the sodium-to-potassium ratio of the blood. Other workers have reached the same conclusions in animals and O'Donnell and associates found similar cytologic changes following administration of ACTH and cortisone in humans prior to death (3, 7, 101, 130).

It is apparent that the question raised by these experiments is of crucial importance in the consideration of the endocrine regulation of electrolyte balance. There are those who feel that this independence of the electrolyte-regulating portion of the adrenal does not apply to the human. Part of this belief is based on the powerful sodium retention which has frequently been demonstrated in connection with ACTH treatment (59, 172). This sodium-retaining effect of ACTH is much more prominent in the human than in the rat (98). Conn and others have felt that the changes in thermal sweat composition which resulted from ACTH treatment and surgical operations were indicative of the operation of a "desoxy" type compound (29, 99). Similarly Leaf and Coulter concluded that pituitary corticotrophic function was mobilized in response to electrolyte demands from experiments in which nitrogen excretion was found to increase as a result of the imposition of a low sodium diet (107). Nevertheless Daughaday found no increase in urinary glycocorticoid excretion in hypertensive patients on low sodium diets such as one would expect if ACTH were mobilized in response to demand for sodium retention (35). Our experiments dealing with the effects of altering sodium and potassium intake would justify similar conclusions (see below).

Brief mention should be made at this point of the main pathways for metabolism and excretion of the major groups of cortical steroids in view of the studies to be reported involving the measurement of excretion products. The glycocorticoids, at least in part, are excreted unchanged except for conjugation. The known conjugates are sulfates and glucuronides. Little is known about the metabolism of mineralocorticoids. However, Cuyler and Hamblen in this country and independently Westphal in Germany showed that 11-desoxycorticosterone was excreted in the urine as pregnanediol glucuronide (34, 74, 184). Hence the following transformation is presumed to take place in the body prior to renal excretion:



11-desoxycorticosterone

pregnane-3α -20α-diol

This phenomenon has been confirmed and a mechanism for the transformation suggested (87, 89). Androgens are excreted as 17-ketosteroids. One cannot, however, assume that the precursors of all urinary 17-ketosteroids are androgens, since glycocorticoids of the cortisone type have been shown to be partially metabolized by this route (170).

VI. THE ADRENAL CORTEX AND WATER METABOLISM

The behavior of the adrenal hormones with respect to the excretion of water is complex and only the essentials of the exceedingly vast and interesting data available on this matter can be discussed. The subject has been very thoroughly dealt with in the reviews by Gaunt and his colleagues (66, 67).

Accompanying the retention of sodium which attends the administration of certain adrenal hormones, there is frequently seen a concomittant retention of water. This is true not only for desoxycorticosterone, but for cortisone and ACTH. If, on the other hand, one considers the effects of adrenal substances on water balance alone, it appears to be one of promoting diuresis. Adrenalectomized animals and Addisonian patients are unable to respond adequately to an administered water load. This, of course, if the basis for the Robinson-Kepler-Power "water test" for adrenal insufficiency (138). Adrenal hormones are able to restore the adrenal-deficient organism to normal in this regard and to enhance the diuretic response to water. Glycocorticoids possess this activity to a much more prominent degree than does desoxycorticosterone. The action of these substances is believed to be one of inhibition of tubular reabsorption of water, though acceleration of glomerular filtration may also be a factor (66, 67). In the mediation of these effects on the kidney, an antagonism to the effects of neurohypophyseal antidiuretic hormone is involved, though whether this antagonism involves changes in sensitivity to antidiuretic hormone, or alterations in production or destruction of ADH is not clear. There is also evidence that the adrenal effect on water metabolism is not limited to the kidney. Effects on water distribution have been shown in nephrectomized animals, and recent evidence has suggested an effect on red cell volume which may be a reflection of generalized activity on cell permeability (131, 152).

Of particular interest is the effect of adrenal hormones on water intoxication. Since the initial studies of Weir and Rowntree, it has been recognized that excessive administration of water to men or animals causes severe central nervous system impairment, typically characterized by convulsive seizures (69, 70, 142, 143, 182, 183). Early work also showed that not only excess of water, but depletion of extracellular electrolytes are factors in the genesis of this state (154, 175). The response of the central nervous system cells under these circumstances is apparently related to reduction in concentrations of those extracellular solutes with respect to which a gradient between the intracellular and extracellular fluid

is normally maintained. Under the circumstances of water intoxication, functional impairment occurs resulting from the movement of water to the interior of the cell following dilution of extracellular ions. This is in accordance with the hypothesis of Darrow and Yannett which states that fluid movements between these two compartments are occasioned by the solute concentrations and not the volume of the extracellular fluid (41). It is for this reason that extracellular dilution, whether it results from an excess of water or a deficiency of salt has the same functional effect.

Adrenal function plays a critical role in the matter of susceptibility to water intoxication. Adrenalectomized animals are extremely susceptible to the damaging effects of water excess. On the other hand, as Gaunt, Swingle and others have shown, by administration of adrenal hormones animals can be made completely resistant to water intoxication (63, 64, 65, 81, 161). This effect of adrenal hormones on inhibition of convulsions resulting from water-loading was first shown to operate in the human by McQuarrie (120, 121, 122). Glycocorticoids are much more potent in this type of activity than are hormones of the "desoxy" type. The possible role of adrenocortical function comes into consideration here because of the high incidence of water intoxication which we have observed in the first two days after operations (see below).

VII. THE PROBLEMS

It is apparent from the data which have been mentioned in the foregoing review that electrolyte balance in the postoperative patient is at least partially under the influence of non-specific factors which are involved in the reaction of the organism to trauma. To an extent which at present is undetermined, these factors are manifestations of activity on the part of the endocrine system. If this is the case, the management of postoperative complications of electrolyte balance will eventually involve not only problems of replacement of water and solutes, but an attack on the basic regulatory mechanisms. In order for this to be feasible a great deal of information will have to be gained regarding the specific endocrine

substances involved, the factors regulating their action, the duration of their activity and the means by which their activity can be altered if indeed the indication for deliberate alterations can be shown to exist.

It was mentioned that mineralocorticoids of the 11-desoxycorticosterone type released as a result of pituitary corticotrophic stimulation have been implicated as being responsible for the characteristic postoperative retention of sodium and loss of potassium. If this is true, the independence of the salt-retaining portion of the adrenal which Greep has demonstrated in the rat must not hold for the human. Such an hypothesis requires that experiments be done to determine whether such a fundamental difference between man and the rat exists. If possible it would also be extremely important to demonstrate the presence of desoxycorticosterone or a metabolite of this substance in the urine of postoperative patients. This should be done by a chemical rather than a biological method since many substances not primarily concerned with mineral metabolism may show sodium retention as a part of their physiological action.

The depression of electrolyte concentrations which has been recorded after operation seemed to deserve study. To what extent is this a constant phenomenon? Is it by itself an adequately frequent and profound deviation to account in part for the usual postoperative alteration in sodium and chloride balance? Is this phenomenon serious enough to be responsible for postoperative symptoms?

The studies which follow represent initial attempts to explore some of these questions. Although it is felt that they shed some light on these basic problems they do not, of course, leave them conclusively answered. Many more studies and much more complex methods will eventually be required.

METHODS

I. EOSINOPHILS

The method most frequently employed for measurement of glycocorticoid function in the studies which follow is the total blood eosinophil count. In the earlier work the eosin-acetone technique of Dunger was employed (46). Later Randolph's phloxine-methylene blue method was adopted (135). Actually there appeared to be very little difference in either precision or reproducibility between the two methods.

II. FORMALDEHYDOGENIC CORTICOIDS

Where output of corticoids was to be determined, Mason's modification of the method of Corcoran and Page was employed (115). This method depends on the oxidation of ketol side chain at carbon-17 to formaldehyde. The formaldehyde is measured by colorimetric reaction with chromatropic-acid, there being a mol-for-mol relationship between the formaldehyde produced and the amount of original steroid. It is important that since this method requires only the presence of the ketol side chain, it is not necessarily specific for glyco- or 11-oxycorticoids, although it is frequently interpreted as a measurement of these substances. The conjugates were hydrolyzed by acidification of the urine to pH 1.0 for 24 hours. The extraction was greatly facilitated by the use of the Cohen continuous liquid-liquid extractor by means of which the acidified urine was extracted for 24 hours with chloroform (24). This technique, though it has been generally accepted, probably measures only a small fraction of the total urinary corticoids since acid hydrolysis releases only the sulfate-conjugated steroids and little if any of the material which exists in the form of glucuronides.

III. PREGNANEDIOL

In the experiments which are described in the latter portion of this report, pregnanediol excretion was studied in male patients after operations. For this a number of methods were tried. The only method which appeared to be capable of

giving significant measurements of the small amounts of this material in male urine was a modification of Guterman's method which was described by Hoyt and Levine (73, 93). Volumes of 500-800 ml. of urine were acidified and refluxed with toluene for one-half hour. The toluene extract was decolorized and evaporated to dryness. The residues were dissolved in acetone and the pregnanediol fraction precipitated with sodium hydroxide. The precipitate was estimated by development of the characteristic red-brown color with sulfuric acid. The Evelyn photoelectric colorimeter was used for all colorimetric determinations. It is appreciated that all "pregnanediol" fractions probably contain steroids which are not the well-known pregnane-3α-20-αdiol. The results of these experiments are therefore significant only insofar as the excretion values after surgery and various other types of treatment are compared with the control values. In later experiments some preliminary studies were done using a pregnanediol assay based on enzymatic hydrolysis of conjugates as developed by Cohen (23).

IV. ELECTROLYTES

Estimation of sodium and potassium concentrations were made by either the Barclay or the Perkin-Elmer flame photometer using the lithium internal standard principle. Carbon dioxide combining power of the plasma and plasma and urinary chloride levels were determined by the usual clinical laboratory methods (132).

V. FLUID THERAPY OF PATIENTS UNDER STUDY

The administration of fluid and electrolytes to these patients followed the principles which have been the routine on the surgical services of this hospital (180, 181). In general, sodium chloride was not given on the day of operation and rarely more than 4.5 grams on the first postoperative day. On subsequent days sodium chloride was given in amounts calculated to replace abnormal losses. In most instances where analyses of externally-lost fluids were not made, about six grams

of sodium chloride was administered for each liter of material lost, such as gastric suction drainage. After the second postoperative day it was customary to give 2-4 grams of potassium chloride by parenteral route. Water was administered in the form of 5% glucose solution allowing 2500-3000 cc. for the total of expected urinary output and insensible loss. To this was added volume-for-volume replacement of external gastrointestinal loss. The state of hydration was further evaluated by daily estimation of the body weight as described by Wangensteen, using the litter balance where patients were unable to stand on the regular scales.

Unfortunately relatively limited facilities for flame photometric determinations and the absence of a metabolic ward rendered overall balance experiments impossible on most of the patients who were studied. It has been necessary to assume that the characteristic changes for example in sodium and potassium balance which have been repeatedly reported by others (see above) applied at least qualitatively to our patients.

EXPERIMENTAL STUDIES

I. RESPONSE OF BLOOD ELECTROLYTE CONCENTRATIONS, WATER BALANCE AND THE PITUITARY ADRENAL-MECHANISM TO SURGERY

It has been mentioned above that what might be called the "normal" postoperative course is characterized by relative hypochloremia and other evidence of dilution of the major extracellular electrolytes. It was of interest therefore to study in some detail the day-to-day course of these levels in uncomplicated cases and to investigate what chronologic correlation existed between these levels and the total eosinophil count as an index of the pituitary-adrenal response to stress. These values were also correlated with the body weight which, over short periods, we feel to be a reliable indicator of the state of water balance. These determinations were done serially in order to determine with what degree of constancy changes in these quantities occurred, the average degree and duration of deviation from preoperative control values and what, if any, relationship in time existed between endocrine activity, water balance and alterations of ionic composition.

A. Course of eosinophil count, ionic concentrations and water balance following standard operations.

The first group studied consisted of 40 patients who underwent operations ranging in gravity from inguinal herniorrhaphy to total gastrectomy. Daily sodium and potassium determinations were done on 15 of the patients. The remaining determinations were carried out on all 40. None of these patients developed clinical complications nor deviations of electrolyte balance which required specific treatment. Figure 2 shows the mean values along with standard errors of the means (X2) of the eosinophil counts, body weight and levels of Cl^-, HCO_3^-, Na^+ and K^+ for the first six postoperative days. It is apparent that the eosinophils fall immediately, their lowest concentration being reached on the first postoperative day. From this point they gradually rise attaining the preoperative value between the fourth and sixth day after operation. Concentrations of sodium and chloride also fall immediately. Sodium values rise again somewhat more rapidly than do the chloride levels. This difference between the response of sodium and chloride is reflected in a tendency toward metabolic alkalosis which is indicated by the slightly elevated bicarbonate levels which are present from the second to fifth postoperative day. Potassium concentrations regularly fall and tend to be depressed throughout the entire interval which was considered in this study.

The electrolyte picture which develops immediately subsequent to surgery is one of dilution of the extracellular ions despite a specific tendency to the retention of sodium and chloride. A partial elucidation of this apparent dilution may exist in findings with regard to the body weight (Figure 2). Under circumstances where nutritional requirements are not met, one would expect a consistent fall in the body weight. In contrast it is observed here that the weight does not fall until after the second postoperative day. On the portion of the graph depicting body weight changes, two other curves are illustrated. One is constructed from the data on fasted, hydrated man studied by Benedict and shows the striking weight

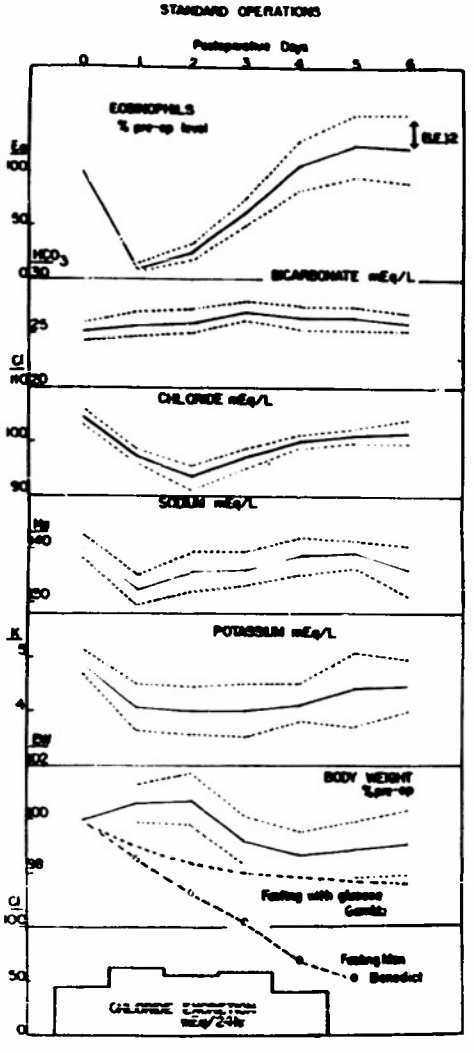


Figure 2. Course of eosinophils, blood electrolytes and body weight changes in 40 cases of uncomplicated elective surgery. (Na and K on 5).

$$\text{wt} = \frac{\text{wt. at time } t}{\text{pre. op. wt.} - \text{specimen wt.}} \times 100)$$

decrease which occurs under these circumstances (10). The second is calculated from Gamble's figures dealing with the effects of 100 grams of glucose on preventing the loss of intracellular and extracellular water which occurs during fasting.* (Larger amounts of glucose produce no greater effect) (62). Since all these patients received at least 100 grams of glucose daily the Gamble curve is surely the more valid "base line" to use in assessing the degree of abnormal water retention which these patients manifested. Even this is only a rough approximation since it is based on the protoplasmic losses which occur as a result of fasting done and does not take into account the greater loss of intracellular protein which occurs after trauma.

The tendency to relative maintenance of weight in the early postoperative period despite the absence of nutrition is clearly the result of water retention. This in turn must be at least partially responsible for the apparent dilution of extracellular electrolyte.

Table I gives the types of operations which were studied along with the duration of eosinopenia and the maximum recorded change in sodium, chloride, potassium and bicarbonate in each case. It is apparent from this that the above-mentioned changes do not depend on the anatomic system operated upon, (G.I. tract, skeleton, etc.); and they are seen with very small procedures (e.g. herniorrhaphy). It also seems that within the range of procedures represented in this group one cannot relate the degree of deviation of electrolyte concentrations to the gravity of the operation. Unquestionably, however, such a relationship would appear if an extremely large number of cases were studied. The following studies show that the magnitude of the procedures does play a role.

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* The actual weights of Gamble's subjects were not given.

B. Course of eosinophil count, ionic concentrations and water balance following highly radical cancer operations.

In a second series a smaller number of cases was studied consisting of highly radical procedures for the treatment of cancer. Ten of these were patients who underwent the operation now designated as "super-radical mastectomy" (179). The remainder were extensive abdominal procedures involving multiple resections and anastomoses, partial resections of the liver and so forth. As in the previous series only cases were included wherein no clinically-evident complications occurred. Since much complications of varying severity are rather frequent following operations of this sort it was difficult to collect an uncomplicated series.

Table II gives the maximum postoperative deviations in this series and Figure 3 shows graphically the course of the various quantities studied with the mean values for the standard-operation series plotted for comparison.

It is of interest in comparing the two groups that there is no significant difference between the pituitary-adrenal response insofar as can be judged from the eosinophil count. The initial drop and duration of eosinopenia are ertirely similar. This, of course, is only true where complications do not supervene. Where serious complications occur, we have frequently observed that the eosinophils remain depressed for many days, sometimes until the patient's death.

Certain quantitative differences, however, appear between the group of standard operations and group of extensive procedures. Chloride and sodium concentrations tend to drop lower and remain depressed for longer following the large operations. Abnormal water retention exists for a longer period as indicated by a failure of the body weight to start falling for an average of three days as compared with two days in the standard-operation group. There appears therefore in the second group to be an exaggeration of the phenomena of water-retention and dilution without any evidence of greater pituitary adrenal activity as far as can be judged by the eosinophil count.

TABLE I

Maximum Deviations of Bicarbonate Chloride, Sodium, Potassium and Eosinophils Following Standard Operations

	Initials	Hosp. No.	Operation	CO_2 Pre.-Max. Post.	Chloride mEq/l Pre.-Min. Post.	Sodium mEq/l Pre.-Min. Post.	Potassium mEq/l Pre.-Min. Post	Duration of Eosinopenia (days)
1.	W.M.	798640	Bil.I. hernia	18 - 23	116 - 102	142 - 132	4.7 - 2.8	5
2.	C.K.	645604	F. hernia	30 - 30	103 - 99	142 - 137	4.6 - 3.8	4
3.	F.S.	776154	I. hernia	28 - 38	105 - 93	142 - 135	4.6 - 2.6	4
4.	A.W.	819643	"	27 - 31	107 - 93			4
5.	F.P.	818312	Exp. Lap.	23 - 30	105 - 96			4
6.	H.H.	577845	"	27 - 28	104 - 96			5
7.	A.D.	814372	"	28 - 28	104 - 100	141 - 125	5.1 - 3.1	6
8.	G.B.	812522	Cholecystectomy	28 - 31	104 - 95	146 - 143	4.8 - 4.6	5
9.	E.C.	831558	"	27 - 30	105 - 95	148 - 135	5.3 - 4.0	3
10.	W.G.	784460	Gastrostomy	26 - 31	103 - 96	142 - 130	5.5 - 4.9	4
11.	L.S.	798603	Gastrectomy	27 - 34	106 - 98			6

TABLE I (continued)

12. C.H.	797064	Gastrectomy	25 - 31	109 -- 97			>5
13. W.L.	792280	"	30 - 33	103 - 95			3
14. S.H.	822750	"	28 - 29	104 - 92			>5
15. E.K.	828324	"	22 - 28	99 - 91	132 - 117	4.1 - 3.0	>6
16. J.B.	830050	"	27 - 26	99 - 95			4
17. R.B.	667131	"	26 - 28	107 - 95	143 - 133	5.1 - 4.8	4
18. M.C.	831784	"	25 - 26	109 - 96	140 - 133	4.0 - 3.8	5
19. H.L.	828355	"	23 - 26	103 - 92	138 - 122	4.9 - 4.3	3
20. L.W.	831860	"	25	103 - 95	134 - 125	4.9 - 4.1	6
21. I.E.	798598	"	20 - 31	110 - 103			6
22. R.B.	819686	Seg. Gastrec.	25 - 29	105 - 91			5
23. H.D.	821026	"	32 - 28	94 - 94			4
24. A.B.	719429	T. Gastrec.	22 - 22	104 - 92			3
25. L.S.	819061	"	23	95			4
26. L.G.	819829	"	104 - 30	102 - 97			4

26 = 1

TABLE I (continued)

27. N.B.	793573	Esophago-gastrec.	26 - 29	104 - 93			5
28. V.N.	821278	"	26 - 29	106 - 94	142 - 129	5.4 - 2.7	4
29. M.R.	822576	Craniotomy	24 - 29	100			4
30. H.A.	816234	"	24 - 30	100 - 92			6
31. L.R.	803253	Rad. Hysterec.	22 - 31	104 - 91			4
32. F.M.	828429	Comb. A.P.R.	27	107 - 98			5
33. C.G.	822138	Lobectomy	22 - 29	105 - 93			4
34. W.C.	800172	Pneumonectomy	22 - 30	102 - 92			4
35. A.L.	800275	Op. Red. Tibia	24 - 31	112 - 99			> 5
36. F.C.	601173	Osteotomy	25 - 26	100 - 96	133	3.4	4
37. J.C.	810803	Sequestrec.	28 - 30	109 - 95	141 - 132	5.1 - 4.2	4
38. W.N.	830721	Sup.Hy.Neck Dis	28 - 27	108 - 100			4
39. M.H.	817978	Glossec. and Mand.	24 - 32	100 - 95			3
40. S.A.	818807	Duod. Pancrea-tectomy	24 - 30	97 - 87			3

It was of interest to determine whether there actually was a significant difference between the electrolyte deviations in the two groups of patients. For this the maximum change from the preoperative value of serum sodium and chloride was considered for each patient. The mean value for these changes in the two groups were found to be as follows:

	Standard Operations	Radical Ca. Operations
Mean max. Cl. changes (mEq/L):	- 8.9	-16.70
Mean max. Na changes :	- 9.3	-15.2

The relative deviate (K) calculated for the two chloride means and the two sodium means where -

$$K = \frac{\bar{x} - \bar{y}}{\sqrt{SE_x^2 + SE_y^2}} \qquad (173)$$

and $\bar{x}$ = mean of standard operation group.

$\bar{y}$ = mean of radical operation group.

SE_x = standard error of standard operation group.

SE_y = standard error of radical operation group.

was found to be as follows:

$$K_{Cl} = 4.0$$

$$K_{Na} = 4.5$$

These values of the relative deviate indicate that in the instances of both the sodium and the chloride changes, there is a probability of less than .001 that the differences which were observed between the standard operation and the radical operation groups was due to chance.

TABLE II

Maximum Deviations of Bicarbonate Chloride, Sodium, Potassium and Eosinophils Following Radical Cancer Procedures

Initials	Hosp. No.	Operation	CO_2 Pre.-Max.Post.	Chloride mEq/l Pre.-Min.Post.	Sodium mEq/l Pre.-Min.Post.	Potassium mEq/l Pre.-Min.Post.	Duration of Eosinopenia (days)
1. C.H.	814408	Super-Rad. Mastec.	25 - 27	102 - 97			5
2. C.L.	814780	"	32	83			4
3. R.T.	223301	"	22 - 27	107 - 83			4
4. F.B.	828485	"	24 - 25	104 - 91	131 - 121	4.4 - 3.8.	>6
5. M.D.	828840	"	24 - 31	105 - 89	136 - 125	4.2 - 4.2	5
6. E.E.	833563	"	24 - 29	106 - 99	150 - 130	5.2 - 4.4	3
7. M.H.	817827	"	28 - 26	104 - 76	116	4.3	6
8. C.W.	840587	"	30	89	145 - 133	2.9	5
9. H.H.	818865	"	25 - 26	103 - 82			>6
10. G.S.	806161	Rad. Abdom. procedures (See text)	25 - 26	106 - 91	141 - 121	4.1 - 2.8	>6

TABLE II (continued)

11. M.H.	814435	Rad. Abdom. Procedures (See Text)	30 - 29	96 - 87	135 - 120		3
12. M.H.(2)	"	"	24 - 35	97 - 77	142 - 126	4.2	4
13. D.D.	832861	"	20 - 25	98 - 79	129	4.3	>6
14. F.C.	808701	"	25 - 38	103 - 73	131 - 117	4.1 - 2.8	3
15. N.M.	818826	"	26 - 26	103 - 91			6
16. J.J.	746099	"	28 - 34	105 - 88	142 - 133	4.5 - 3.9	5

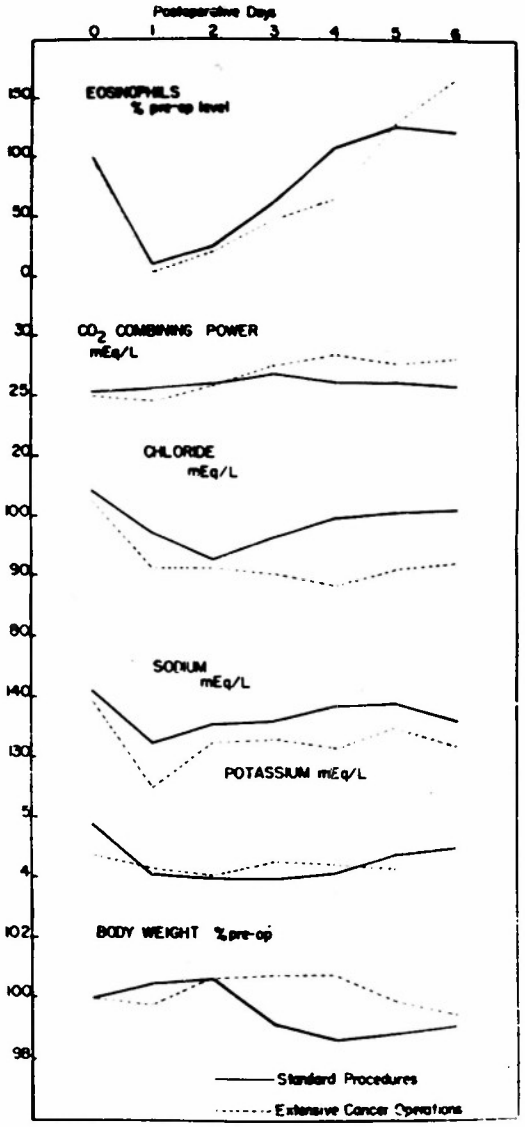


Figure 3. Course of eosinophils, blood electrolytes and body weight changes in 10 cases of extensive cancer surgery compared with similar data from standard operations.

II. WATER INTOXICATION FOLLOWING SURGERY

Twenty patients were studied in whom it was possible to relate the occurrence of very striking central nervous system signs to postoperative dilution of the extracellular electrolytes. The findings are presented here because they represent an important consequence of the postoperative tendency to water retention and electrolyte dilution and because of the relationship between susceptibility to water intoxication and adrenal function which has been shown experimentally.

The relationship of convulsions to the state of hydration has long been recognized. The patients which Weir and Rowntree originally described were individuals with diabetes insipidus to whom water was forced after they had been adequately treated with posterior pituitary extract. The syndrome was first described in a surgical patient by Helwig in 1935 (85). Barahal reported its occurrence in a mental case, and recently the situation has been described as a complication of massive enemas in cases of Hirschprung's disease (8, 86). Ariel and Kremen in this department described the occurrence of greatly enlarged thiocyanate spaces in certain surgical patients in two of whom convulsions were seen (4).

A. Clinical Data

The clinical data on twenty patients who developed severe central nervous system signs postoperatively are given in Table III. Eighteen had generalized seizures; the other two merely exhibited sudden loss of consciousness. Ten of the twenty cases followed abdominal operations. Four followed operations on the breast and chest wall. Two operations involved head and neck and two the extremities. There appeared to be no predilection for operations involving a single anatomical region or system. The symptoms and signs ranged in severity from a single convulsion followed by complete recovery to numerous seizures with coma or confusion lasting 10 days. Two patients in the series died and in one there appeared to be no demonstrable cause of death beyong the disturbance of hydration.

B. Time of Onset of Water Intoxication

Figure 4 shows the distribution of times of onset of seizures or coma with reference to the time of operation. It is of considerable interest that 17 of the 20 cases occurred in the first 48 hours and the majority in the 12-to-36 hour interval. It is significant that, as has been pointed out above, this is the period following operation in which the extracellular sodium and chloride values are normally found to be at their lowest.

C. Water Balance

Table IV gives the intake and output data and changes in body weight recorded in the 20 cases of water intoxication. It is apparent that 6 of the cases received unusually large amounts of water, (4000-5000 cc.) whereas the remainder received rather reasonable quantities (2500-3500 cc.). In no instance, however, were the amounts of water given in excess of the quantity that could be tolerated by normal individuals who had not undergone surgery. The clinical aspect of the postoperative intolerance to water is thus illustrated. The changes in body weight from the time of surgery to the onset of symptoms are also given in Table IV, wherein it can be seen that in 14 of the cases a significant increase in weight of more than one kilogram was observed.

D. Electrolyte Concentrations

Although evidence of positive fluid balance was not an entirely constant finding in this group of patients, severe depression of major extracellular electrolyte concentrations was seen in every case. This again is reminiscent of the uncomplicated postoperative cases in which some reduction of the extracellular sodium and chloride concentrations was seen in every single instance. These findings are tabulated in Table V which shows that the majority of sodium values were below 125 mEq/l and that 19 of the 20 chlorides were 85 or lower, the majority being lower than 80. The mean chloride and sodium concentrations at the time of onset of seizures were 78.4 and 117.1 mEq/liter respectively.

TABLE III

Clinical Data in 20 Cases of Postoperative Water Intoxication

Case No.	Patient Date	Sex Age	Diagnosis and Operation	Onset of Convulsions (hr. after Operation)	Clinical Signs	Systolic Blood Pressure 1. Pre-op. 2. Seizure		Temperature (in Degress F.)	Outcome
1.	M.M. 793005 7/30/48	F 74	Ca. rectum; combined excision	31	Unconsciousness, seizures involv. sep. extremities, never generalized	140	152	98.6 (axillary)	Confusion 10 days complete recovery
2.	G.B. 794999 9/29/48	M 68	Diverticulitis; partial colectomy	26	2 seizures, coma, areflexia	155	190	99	Coma 4 days, followed by confusion & hallucin., memory impairment; eventual recovery
3.	E.T. 797761 11/26/48	F 68	Ca. Breast; superrad. mastectomy	40	Cyanosis & Stupor, generalized seizure, hyporeflexia, Babinski's sign	150	168	101	Death in 12 hr.
4.	J.S. 611953 6/17/49	F 77	Ca. rectum; ant. resection	23	2 seizures, coma, Babinski's sign (?)	170	240	98	Coma 4 days, complete recovery; reop. 6 mo. later well tolerated
5.*	J.J. 729986 7/28/49	F 72	Ca. stomach; gastrectomy, cholecystectomy, nephrectomy	31	Gen. seizure, coma, Babinski's sign	140	118	99.8	Mental recovery in 10 days
6.*	A.L. 805574 8/3/49	M 82	Stomach ulcer; gastrectomy	26	Unconsciousness preceding 2 seizures	124	130	100	Coma 2 days followed by confusion, recovery in 1 week

TABLE III - Continued

7.	M.H. 798609 8/29/49	F 68	Ventral hernia	31	Confusion followed by seizure & coma	160	130	99.2	Mental recovery in 48 hr., complete recovery
8.	F.C. 808761 9/15/49	M 72	Ca. stomach; subtot. gastrectomy, part. pancreatectomy, colostomy	41	1 gen. seizure, loss of consciousness	120	104	100.8	Return consciousness 1 hr., complete recovery; re-explor. 2 mo. well tolerated
9.	B.B. 810020 10/14/49	F 76	Ca. rectum; combined excision	26	Gen. seizure, coma	130	160	98.9	Coma 24 hr. followed by confusion, recovery 1 wk.
10.	M.H. 817978 5/19/50	F 53	Ca. tongue; gastrostomy	15	2 grand mal seizures, coma, hyperreflexia, no Babinski's sign	150	135	100	Recovery 24 hr., further surgery well tolerated
11.	E.W. 825320 11/14/50	F 59	Recurrent ca. breast; excis. chest wall tumor	27	7 gen. seizures, coma, areflexia, no Babinski's sign	180	180	101	Profound coma 6 days, disorientation; ment. recov. 1 mo., memory defect persists
12.	D.S. 785066 4/16/51	F 38	Osteomyelitis, amyloidosis with renal involvement; excis. of sinuses	48	2 gen. seizures with rapid return of consciousness	130	120	98.4	Recovery from episode; death 3 wk. later from uremia
13.	H.H. 831326	F 76	Femoral fracture; internal fixation colostomy	11	Confusion & twitching movements 8 days preceding convulsion	110	124	100.8	Treatment caused diuresis and wt. loss, but patient died in 12 days
14.	I.F. 832284 5/17/51	F 55	Ca. breast; super-rad. mastectomy	32	1 gen. seizure	180	150	101.4	Coma 2 days, grad. ment. recovery, memory defect persists

TABLE III - Continued

15.	L.W. 831860 5/29/51	F 63	Ca. stomach; gastrectomy	21	1 gen. seizure,	140	160	99.5	Return of consciousness in 5 hr., complete recovery
16.	R.G. 832606 7/6/51	F 71	Ca. breast; rad. mastectomy	22	1 seizure, coma reflexes normal no Babinski's sign	140	160	102	Coma 2 days, confusion 3 wk., slight memory impairment, recovery otherwise
17.	A.O. 833708 7/6/51	M 74	Ca. stomach; gastrectomy	19	1 gen. seizure, coma, Cheyne-Stokes respiration	148	130	101.3	Return of consciousness in 10 hr., death 5 days later from failure of anastomosis to heal
18.	E.L. 842959 3/26/52	F 71	Ca. colon, right colectomy	36	Stupor, coma, eye deviation, Babinski's sign	175	130	100.2	Consciousness & neurological signs, normal in 2 days
19.	G.H. 846445 7/13/52	F	Ca. parotid; parotidectomy & neck dissection	78	Confusion, coma, Babinski's sign	120	144	98.6	Mental & neurological recovery in 24 hr.
20.	E.C. 854886 3/2/53	F 71	Ca. bladder, cystoscopic fulgeneration	37	Grand mal seizure, coma	122	100	101.2	Mental recovery 48 hr.

*Cases previously reported by Ariel and Associates in paper dealing with enlargement of thiocyanate space.

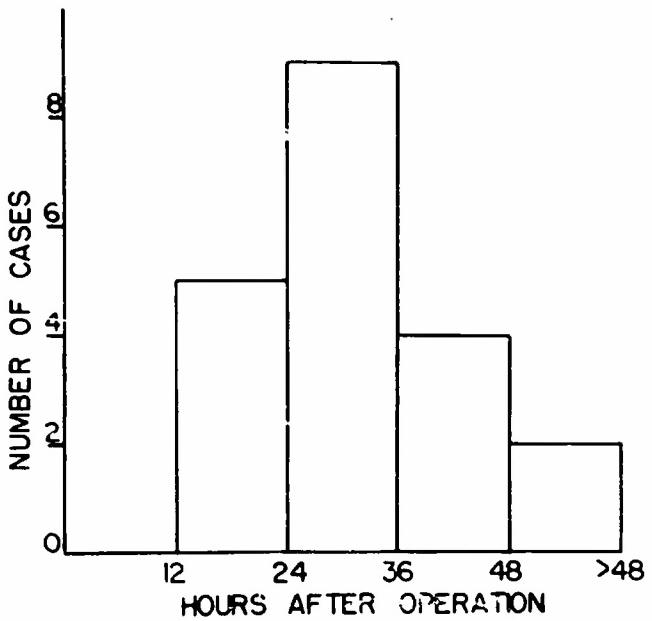


Figure 4. Distribution of times of onset of seizures after operation in 20 cases of post-operative water intoxication.

E. Mechanism of Physiologic Disturbance in Water Intoxication

The experimental work on water intoxication has repeatedly shown that the inclusion of sodium chloride in force-administered water will prevent the occurrence of seizures (154, 175). This is not true for substances such as urea and glucose to which the cell membrane is freely permeable. Large concentrations of such substances will not prevent water intoxication.

It would appear therefore that the phenomenon of water intoxication is a functional manifestation of cells behaving in accordance with the hypothesis of Darrow and Yannet which states that changes in intracellular fluid volume are mediated not by the total amount of fluid or electrolyte but only by the effective osmotic tension (and therefore the electrolyte concentration) of the extracellular fluid.

The data on these patients confirm this, for though not all patients received great excesses of water and not all gained weight, the finding of depressed sodium and chloride concentrations in the serum was characteristic of all cases. Thus either an excess of fluid or a deficit of salt can be expected to be equally significant in predisposing to this condition. Case #18 was of particular interest in that the development of postoperative water intoxication was apparently related to the fact that the patient had been maintained preoperatively on a low sodium diet for cardiac disease.

F. Adrenal Function in Postoperative Water Intoxication

Because of the large accumulation of evidence relating adrenocortical deficiency to susceptibility to water intoxication eosinophil counts and epinephrine-eosinophil tests were done on a number of these patients.

Table IV gives eosinophil counts at the time of the seizures and the results of 3 epinephrine tests and one ACTH test all of which were carried out at least 14 days after recovery from central nervous system manifestations. In one case only was the eosinophil count, done at the time of seizure, abnormal. In this case,

TABLE IV

Fluid and Electrolyte Balance in 20 Cases of Postoperative Water Intoxication

Case No.	Patient	Body Weight (in KG.)	Weight of Surgical Specimen (in KG.)	Weight Change from Pre-op. (in KG.)	Fluid Therapy 24 hr. Prior to Seizure	Urine Output 24 hr. Prior to Seizure	Urine Chloride mEq/l	Fluid Therapy Following Seizure	Duration of Abnormal Chemistries
1	M. M.	58.2	.835	⁄1.5	4,075 cc. 5% & 10% glucose	475	41.5	2,000 to 3,800 cc. 5%, 10% & 20% gl. without NaCl daily	10 days
2	G.B.	60	1.53	⁄1.1	3,500 cc. 5% gl.	1,000	142	3,000 to 5,000 cc. 5% gl. daily with 4.5 to 9 Gm. NaCl	10 days
3	E. T.	50.5	1.120	⁄2.5	3,450 cc. 5% gl.	650	12.4	3,200 cc. 5% gl.	Patient died
4	J.S.	54.6	.285	0	3,500 cc. 5% gl.	600	10.7	3,500 cc. 5% gl. with about 15 Gm. NaCl and 1 Gm. KCl daily	3 days
5	J. J.			⁄1.3	3,500 cc. 5% gl.	1,200	57	Fluids limited to 2,000 cc. daily without NaCl	6 days
6	A. L.	40.0	.135	⁄3.2	4,200 cc. 5% gl.	975	80	Fluids limited to 1,500 cc. daily 13.5 Gm. NaCl on 2nd day after seizure	6 days
7	M. H.	56.8		0	3,500 cc. 5% gl.	750		2,500 cc. 5% gl. with 18 Gm. NaCl.	2 days
8	F. C.	47	.185	-1	3,675 cc. 5% gl. with 4.5 Gm. NaCl	1,475	2.6	3,500 cc. 5% gl. with 13.5 Gm. NaCl	4 days

TABLE IV (continued)

9	B. B.	58.0		∱1.0	3,900 cc. 5% gl.	1,100	60.2	3,000 cc. daily with 9 to 13.5 Gm. NaCl	4 days
10	M. H.	43		∱1.5	3,500 cc. 5% gl.	400		1,500 cc. 5% gl. with 13.5 Gm. NaCl	1 day
11	E. W.	58.3		∱2.5	3,500 cc. 5% gl.	1,500	164	3,000 to 3,500 cc. 5% & 20% gl. with 9 to 18 Gm. NaCl. 50 mg. cortisone every 4 hr.	5 days
12	B. S.	49.2		∱4.5	2,500 cc.	450	6	1,000 cc. with 9 mg. NaCl	2 days: patient died of uremia 3 wk. later
13	H. H.	53.8		∱6 in 8 days	1,500 to 3,000 cc. 5% gl. without NaCl	800 (av.)	34-98	2% NaCl	Na & Cl. elevated by therapy, but never reached normal, patient died
14	I. F.	45.4		∱3.8	5,200 cc. 5% gl.	1,650	4 25	27 Gm. 2% NaCl 1,800 cc. fluid	12 hr.
15	L. W.	55.6	.220	∱1.4	3,000 cc. 5% gl.	1,600	5	1,500 cc. 5% gl. with 9 Gm. NaCl	1 day
16	R. G.	55		∱3.6	5,200 cc. 5% gl.	1,000	99	2% NaCl 23 Gm., later: 5% gl. to total 3,400	1 to 2 days
17	A. O.	52.2	.185	∱1	4,500 cc. with 9 Gm. NaCl	3,400	20	1,500 cc. with 4.5 Gm. NaCl	2 days, patient died 5 days later

TABLE IV - (continued)

18	E. L.	54.4	.640	/3.4	3,000 cc. 5% gl.	600	102	10%-20% gl.: 3,000 cc. with 13.5 Gm. NaCl	6-7 days
19	G. H.	50.2		-0.5	2,500 cc. 5% gl.	1,200		500 cc. 3% NaCl	2 days
20	E. C.	44.2	0	/1.5	3,000 cc. 5% gl.	2,050		1,000 cc. 2% NaCl	1 day

illustrated in Figure 5, eosinophil counts and blood electrolyte determinations were being made as a matter of routine. The patient underwent a prolonged and extensive operation. The eosinophil count at the time of the onset of convulsion on the second postoperative day was found to be 100% of the preoperative value. Reference to Figure 1 will confirm the fact that this is in our experience completely out of the range of normal variation in the postoperative eosinophil response. Figure 4 shows the course of the eosinophils and plasma electrolytes in this patient. He received 3600 cc. of fluid during the 24 hours prior to seizure, but did not gain weight. The eosinophil count spontaneously fell again and the patient went on to recovery.

Fortuitously this patient supplied us with some additional information. It happened that his blood for analysis was drawn about an hour before the first convulsion occurred at which time he was apparently in sound condition. This established the fact that the seizures were definitely the result of rather than the cause of the electrolyte disturbance. It is also of interest that this patient survived and underwent another operation six months later at which time the postoperative course was uncomplicated.

All the other patients had eosinophil levels in the range of the normal postoperative pattern, and the epinephrine and ACTH tests in the few instances where they were done, gave no evidence of impaired adrenal reserve (Table VI).

G. Treatment of Postoperative Water Intoxication

Although the treatment and prevention of postoperative water intoxication will not be dealt with in detail, certain observations with regard to the results of therapy are of interest. It is apprent from Table IV that the serum electrolyte values returned to normal most rapidly in those cases in which considerable amounts of sodium chloride were given and fluid intake was rigorously curtailed. This usually required the administration of hypertonic sodium chloride solutions. The number of cases studied here does not permit conclusions regarding the clinical

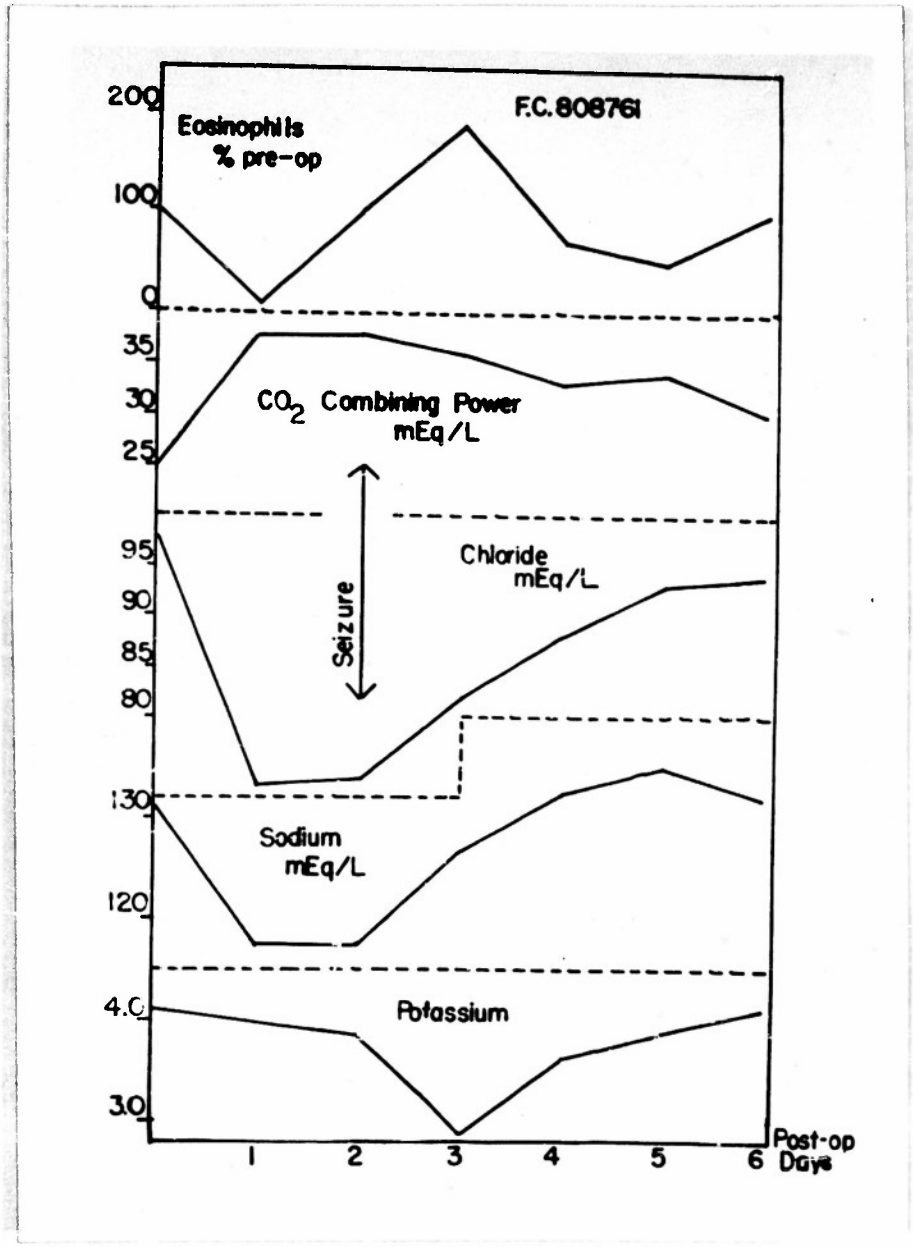


Figure 5. Eosinophil and electrolyte data in 72 year old man who developed seizures following subtotal gastrectomy, pancreatectomy, and colectomy. This is only instance where eosinophils were abnormally high at time of onset of convulsions.

TABLE V

Blood Chemistry in 20 Cases of Postoperative Intoxication

Case No.	Patient	CO_2 Combining Power (mEq/l)	Serum Chloride (mEq/l)	Serum Sodium (mEq/l)	Serum Potassium (mEq/l)	Blood Urea Nitrogen (MG./100 c.c.)	Blood Sugar (MG./100 c.c.)	White Blood Count
1	M. M.	26	74					
		20	66					
2	G. B.	30	80					
		32	68	108	2.2	18		17,400
3	E. T.	22	77			10		20,700
4	J. S.	15	78	126	5.5	40		18,450
5	J. J.	17	83	113	3.9	7	92	14,900
6	A. L.	27	92					
		22	80	122		16		
7	M. H.	27	79			11	106	19,000
8	F. C.	38	74	118	3.9			
9	B. B.	24	81			11		11,300
10	M. H.	15	85			10	167	9,900
11	E. W.	18	74	113	4.3	14	160	8,750
12	B. S.	19	83	125	5	66	94	
13	H. H.	28	53	94	3.1	9		19,350
14	I. F.	17	76	114	3.7	18		
15	L. W.	24	95	133	3.2	9		
16	R. B.	20	83	116	3.1	9		
17	A. O.	16	85	120	3.6			
18	E. L.	28	80	115	3.7	21		
19	G. H.	23	73			6		
20	E. C.	25	83	123	4.0	6		
Mean		23.17	78.35	117.1	3.78	16.52	123.8	

TABLE VI
Eosinophil Data - Postoperative Water Intoxication

Patient No.	Count at time of onset of symptoms (cells/cu. mm.)	Subsequent response to adrenal stimulation
8	93 (same as pre-op.)	
10	0	60% response to epinephrine
11	7	
12	61	
13	10	
14	12	58% response to epinephrine
15	2	
16	7	45% response to epinephrine
18	28	
19	0	
20	0	58% response to ACTH

results of this therapy as compared with other methods. However, in view of the apparent mechanism of the functional disturbances in water intoxication it seems evident that the procedure which restores extracellular electrolyte levels to normal most efficiently is to be preferred. This is particularly cogent in view of the evidences showing that depression of serum chloride and sodium concentration impairs glomerular filtration and therefore water diuresis (5, 17, 86). Figure 6 illustrates the weight changes and depression of electrolyte values in a typical case of water intoxication and the correction which was achieved in a 12-hour period by the administration of hypertonic sodium chloride solution.

III. THE RELATIONSHIP OF PITUITARY CORTICOTROPHIC ACTIVITY TO THE ADRENAL REGULATION OF ELECTROLYTES

The first two studies, those relating to postoperative changes in electrolytes and the studies of water intoxication demonstrated a consistent and occasionally serious reduction of sodium and chloride levels during the early postoperative phase. It is the author's feeling that this phenomenon by itself goes a long way toward explaining the tendency of the postoperative kidney to retain these ions. As has been stated earlier, however, it is generally accepted that the production of adrenal hormones is largely concerned with postoperative sodium and chloride retention and some have implicated those hormones (the 11-desoxy group) which are believed to have as their specific function the retention of sodium (75, 76, 77, 78, 99). At present very little is known about the measurement of endogenous 11-desoxycorticosterones although some attempts in this direction will be mentioned in a later section. A related question, and one of critical importance to the argument can be attacked. We know that the other effects of stress for which the adrenal cortex is responsible are mediated by pituitary corticotrophic activity. Is the production of salt-regulating corticoids in the human under this type of pituitary control? One recalls that the experiments of Greep and his co-workers on the cytologic changes in the adrenal zones indicated that mineralocorticoids

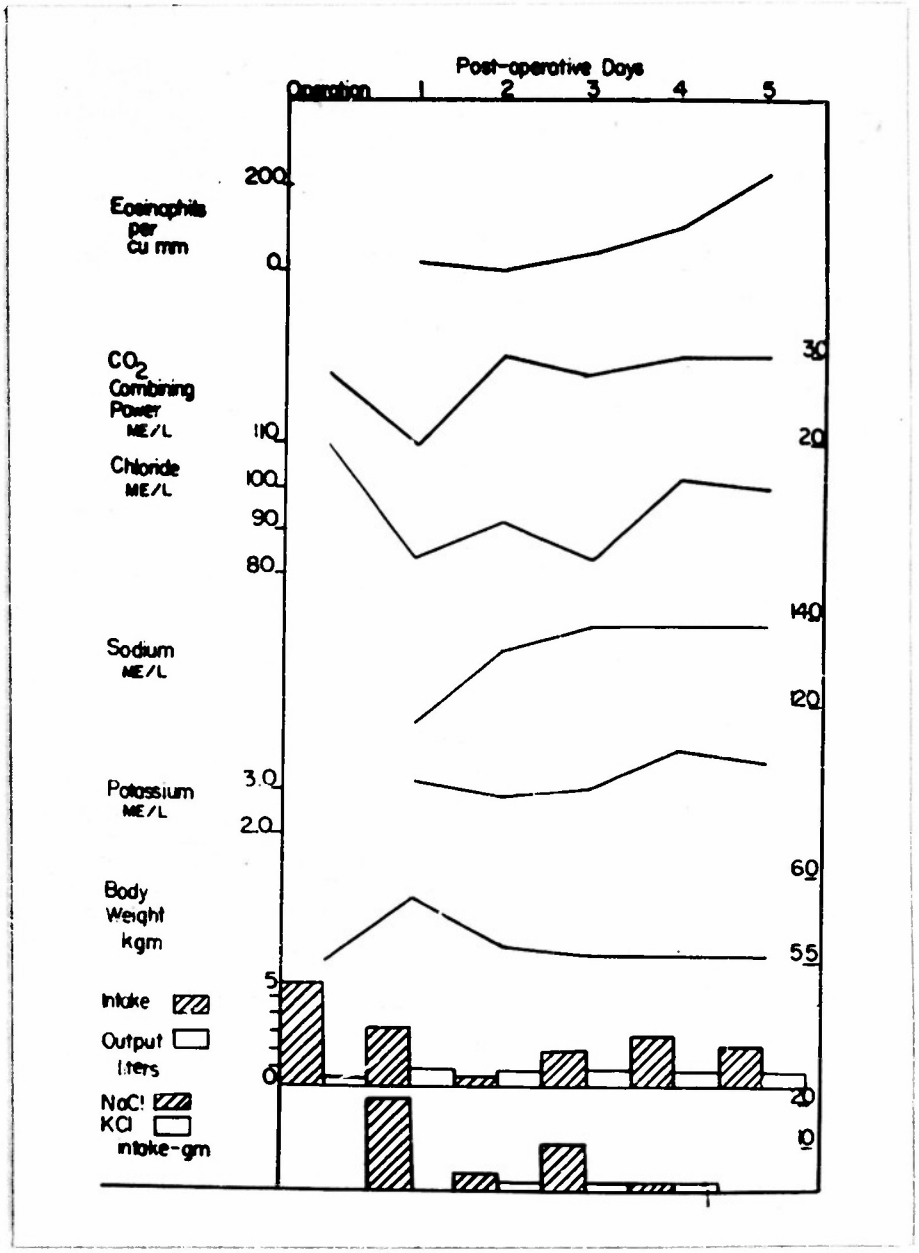


Figure 6. Response to therapy with hypertonic (2%) saline for seizures which began on first postoperative day. Immediate clinical response correlated with elevation of depressed Na and Cl. Gradual onset of diuresis.

were independent of pituitary corticotrophin (42, 71, 72). The experiments of Daughaday on the effects of sodium restriction on the output of corticoids in hypertensive patients would suggest similar conclusions (35). The following experiments were devised to test this relationship in the relatively normal human subject.

The subjects were patients awaiting elective surgical procedures who agreed to take the experimental diet. Patients with acute situations or inflammatory or metabolic diseases were not studied. The experiments consisted simply in placing these subjects on a diet containing 200-250 mgm. of sodium per day. This diet was found to contain an average of 4 grams of potassium ion. The subjects were given in addition 12 grams of potassium chloride in enteric coated tablets. This regime allowed an intake of 9-13 milliequivalents of sodium and 250-30 milliequivalents of potassium ion daily. It was anticipated that such a regime would contribute and "electrolyte stress" adequate to mobilize whatever reactions on the part of the adrenal are necessary when a need for mineral-regulating corticoids exists. The usefulness of the Wilder test, which is based on a less severe stress than this one and the poor reaction which might be expected if an Addisonian patient were exposed to this regime would seem to validate this assumption. To assess pituitary corticotrophic activity, eosinophil levels and urinary formaldehydogenic corticoid excretion were measured.

The effect of the diet on 11 subjects in whom eosinophils were measured is illustrated in Figure 7. In five of these cases, corticoid determinations were also done. These are shown in Figure 8. Electrolyte balance studies were not carried out on the entire group of subjects but the sodium excretion and plasma Na and Cl levels in two subjects on this regime are shown in Figure 9. As would be anticipated, severe curtailment of sodium excretion occurs, but there is little if any reduction in the plasma levels.

It is apparent from the experiments illustrated in Figures 7 and 8 that neither eosinopenia nor increase in glycocorticoid excretion was caused by this

regime. Actually, the eosinophil levels tended to be higher and the corticoid excretion lower during the experimental period. The conclusion is justified that whatever response was made to this "electrolyte stress" did not involve the release of pituitary corticotrophic hormone. Although one cannot step to the converse conclusion that pituitary corticotrophic stimulation does not produce mineralocorticoids, this would seem to be unlikely in view of the data indicating that a physiological stimulus for mineralocorticoid production does not involve the participation of corticotrophic hormone.

IV. THE EXCRETION OF PREGNANEDIOL: AN ATTEMPT TO FIND DIRECT EVIDENCE FOR MINERALOCORTICOID PRODUCTION IN THE POSTOPERATIVE PATIENT

Although the experiments discussed in the previous section suggest that stimulation of the pituitary is not involved in the response to a situation designed to call forth the production of mineralocorticoids, it does not eliminate the possibility that the converse proposition could be true: namely, that stimulation of the pituitary-adrenal axis by stress could result in the production of mineralocorticoids. For this reason, a more direct approach to this question was sought. As has been previously mentioned, the investigation of this point has been hampered by the lack of methods and by our limited knowledge of the metabolism of corticoids, particularly those of the 11-desoxy type.

At the time when this investigation was begun, the only known fact pertaining to the metabolism of 11-desoxycorticosterone was that when the substance was administered to human's and animals, there was an increased excretion of pregnanediol glucuronide (34, 74, 87, 89, 184).

It seemed to be of interest, therefore, to ascertain whether patients excreted an increased amount of preganediol glucuronide following surgery. For this study only male patients were utilized, since it was anticipated that the cyclic production of progesterone would dominate the excretion of pregnanediol in the female.

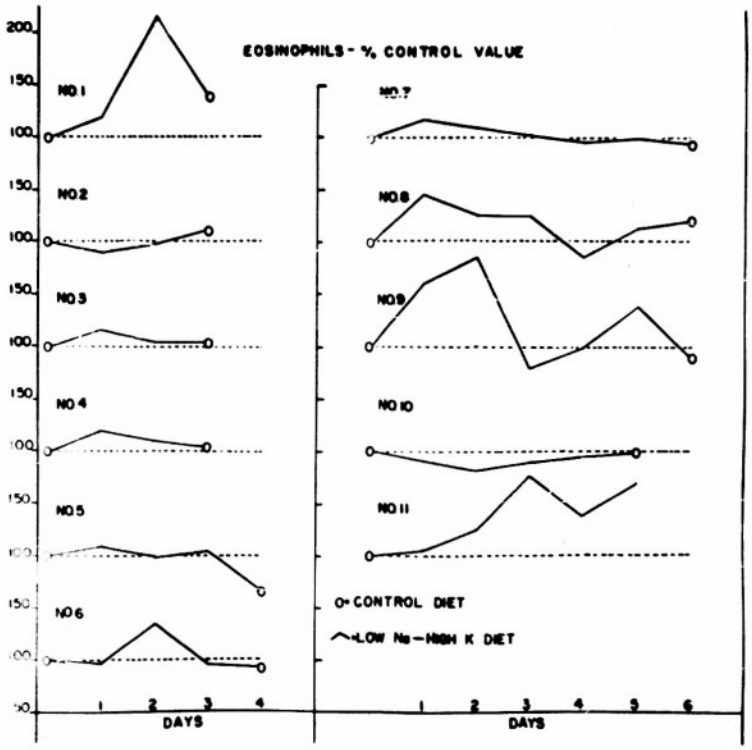


Figure 7. Eosinophil counts before, during and after low Na, high K intake in 11 subjects. O = after at least 24 hours of normal diet.

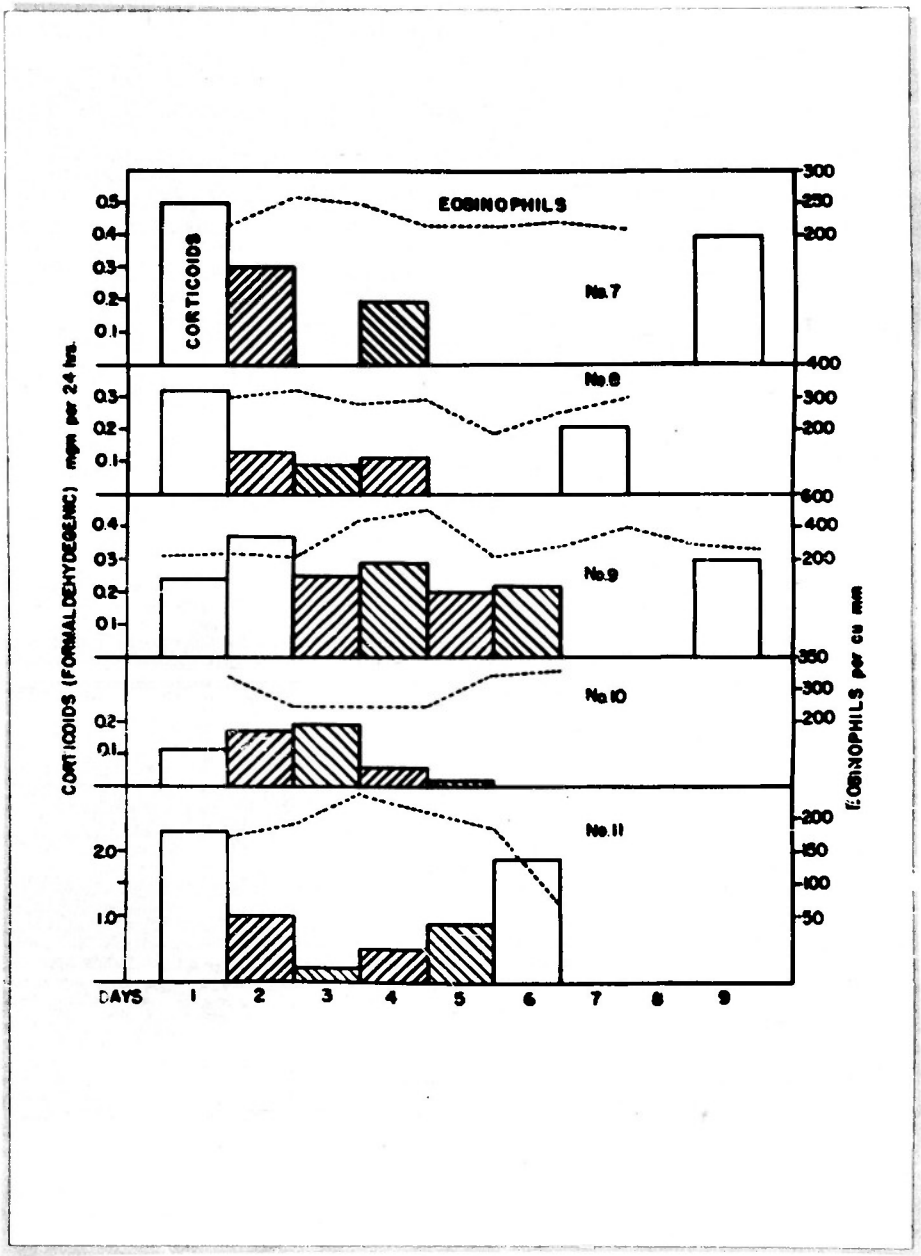


Figure 8. Formaldehydogenic corticoid exoretion in 5 subjects on low sodium, high potassium intake. Cross hatch = experimental diet. Open bars = normal diet.

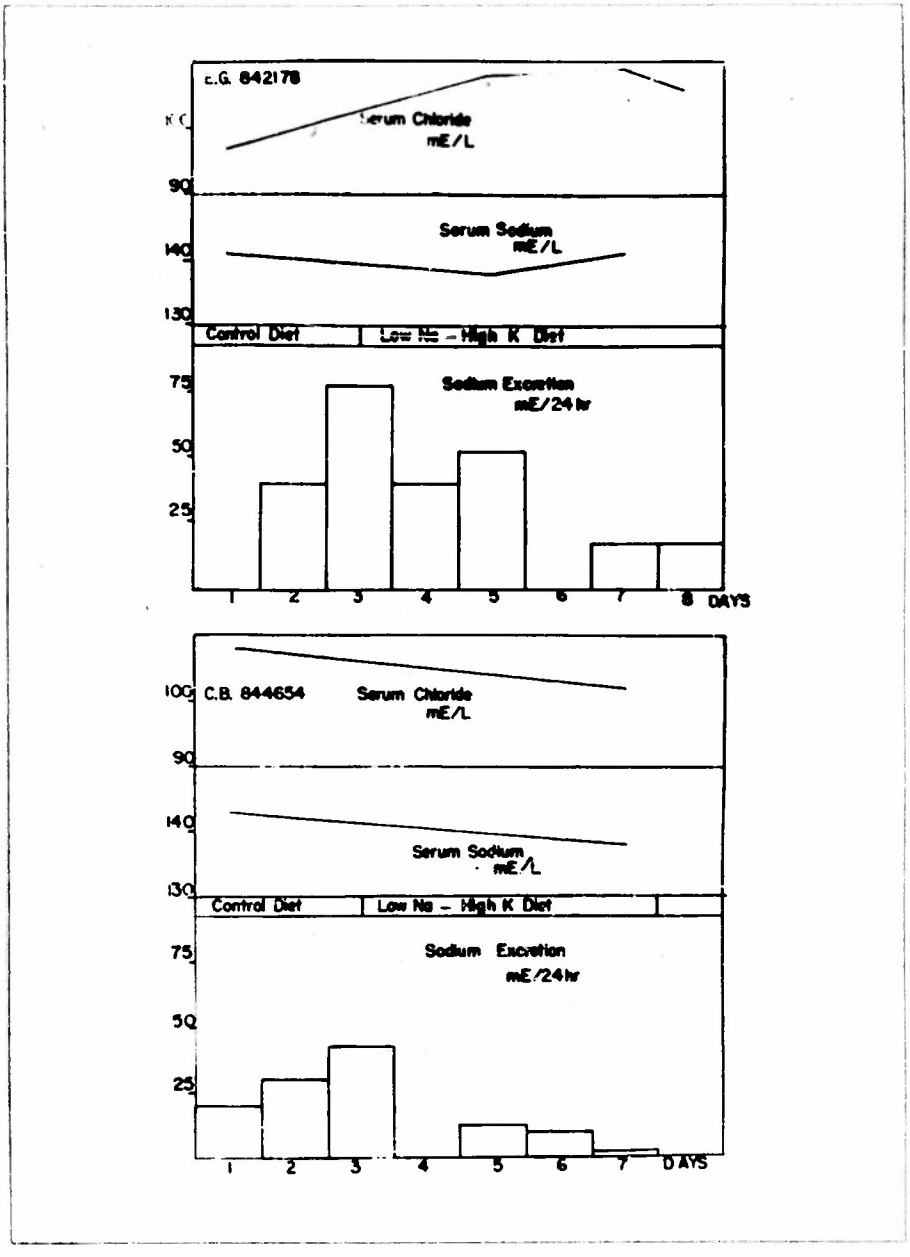


Figure 9. Serum levels and urinary sodium excretion in 2 subjects on low sodium, high potassium intake described in text.

The mean 24-hour excretion of pregnanediol by the method described in 25 male patients awaiting elective surgery and not suffering from inflammatory or metabolic diseases was 0.57 mgm. In comparison, the values on three adrenalectomized patients were of some interest. They are given below:

24-Hour Pregnanediol Excretion (mgm)

Mean of 25 male patients:	0.57 (SD = .424)
Ovariectomized-adrenalectomized female (M.S. 688311)	.05
Ovariectomized-adrenalectomized female (E.W. 763790)	.15
Orchiectomized-adrenalectomized male (P.G. 822436)	.06
Orchiectomized male (W.McG. 852651)	.37

The very low values seen after adrenalectomy would seem to offer confirmatory evidence that a considerable portion of this material is of adrenal origin.

B. Excretion Following Surgical Operations

It was found that in 7 male patients studied, before and after surgical procedures, there was an increase in pregnanediol excretion following operation in all instances. The quantity reached a maximum in the first or second postoperative day, the postoperative excretion being two-to-five times the preoperative value. In general the excretion of pregnanediol ran parallel to that of the formaldehydogenic corticoids and to the depression of the blood eosinophil counts. The course of the three values before and after surgery is illustrated in Figure 10. The formaldehydogenic corticoids were carried out only when the patients excreted adequate amounts of urine for both determinations to be done.

This finding constituted something of surprise, since it was anticipated from the previous experiments involving sodium restriction that, following the stress of surgery, nothing would be excreted save oxycorticoids. However, numerous

explanations for this finding remained. One was that this phenomenon, occurring in relationship to surgery had nothing to do with activation of the pituitary-adrenal axis and was evoked by some entirely different mechanism such as the reduced serum sodium concentration which might independently stimulate the production of a mineralocorticoids. For this reason, similar experiments were carried out in which ACTH administration was substituted for surgery.

C. Pregnanediol Excretion During ACTH Administration

In order to determine whether excretion of the material being measured as pregnanediol could be effected by stimulation of the adrenal cortex without the existence of non-specific stress, the same measurements were done during administration of from 60 to 100 mgm. per day of ACTH. ACTH was given intramuscularly usually in 4 doses throughout the 24 hour period; in one case by 8-hour I.V. infusion. The mean value before treatment (10 observations on 6 patients) was .64 mgm/24 hours. During treatment (11 observations on 6 cases) it rose to 1.35 mgm/24 hours. The individual cases are illustrated in Figure 11 which shows relationship eosinophils and corticoid excretion. It seems justified therefore to conclude that the substances thus measured is either produced by the adrenal or is a metabolite of an adrenal product.

D. Pregnanediol Excretion During Glycocorticoid Administration

It remained to determine whether the excretion of pregnanediol was evidence of the production of something beside glycocorticoids. Was this merely another metabolic pathway common to all adrenal hormones? Consequently, the same measurements were carried out on patients who were receiving glycocorticoids: Compounds E and F. It was found that moderate doses of intramuscular cortisone (less than 200 mgm. daily), gave no increase in pregnanediol excretion. Unfortunately, with such doses significantly high urinary formaldehydogenic corticoids and profound eosinopenia were not seen.

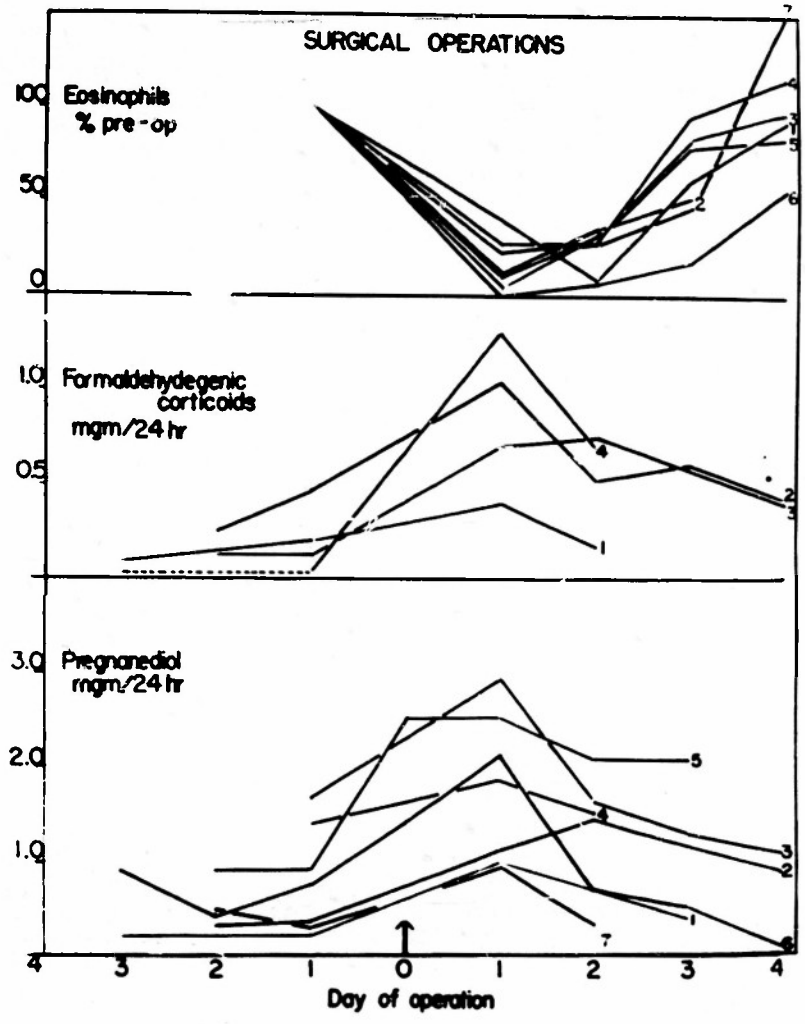


Figure 10. Excretion of material in pregnanediol fraction following surgery and relationship to eosinophils and corticoid output: 1 - Bil. herniorrhaphy, 2 - Comb. proctosigmoidectomy, 3-6 - Gastrectomies, 7 - Colostomy.

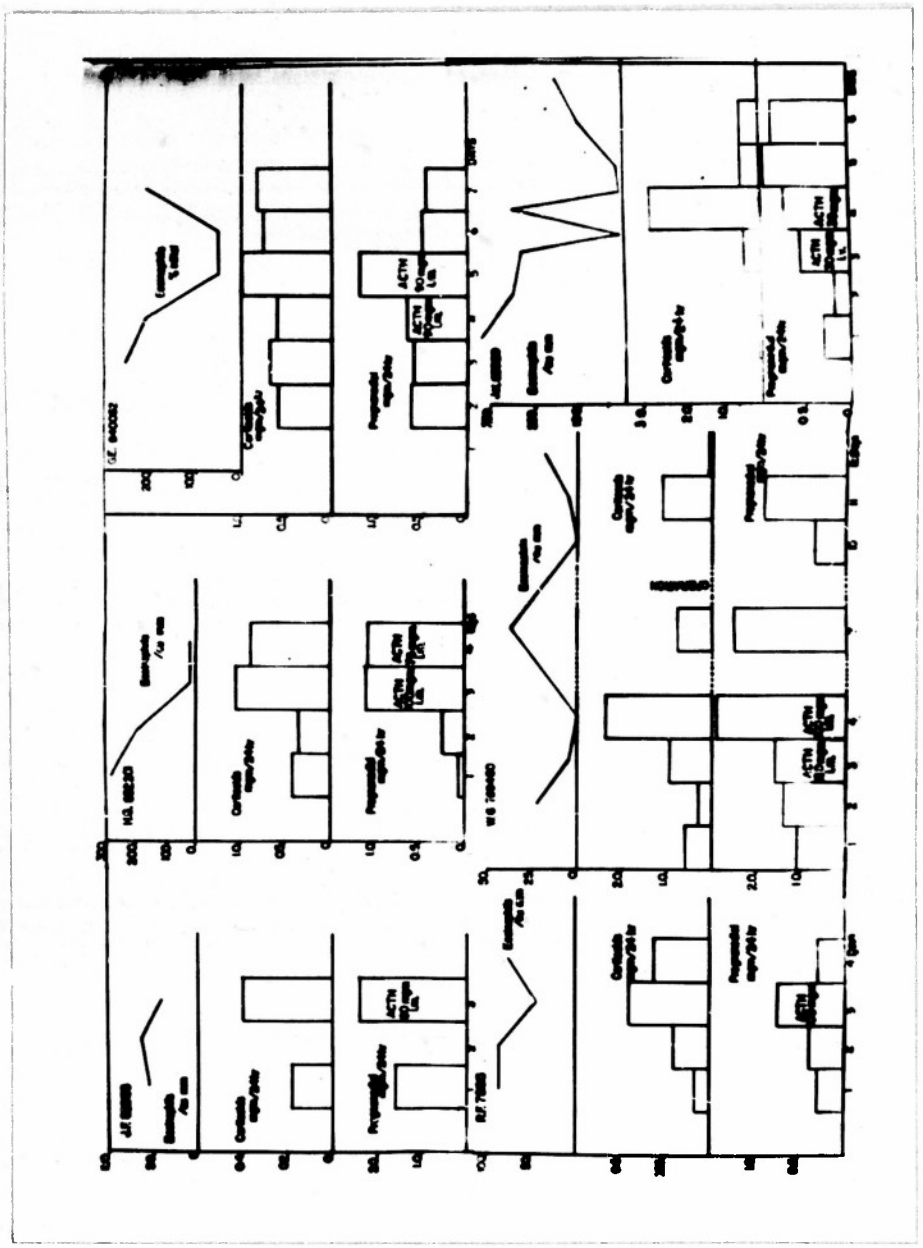


Figure 11. Pregnanediol, formaldehydrogenic corticoids and eosinophils during ACTH administration in 6 patients.

When, on the other hand, relatively large doses of cortisone were used or when the material was given by mouth, a more effective route of administration, definitely elevated levels of urinary formaldehydogenic corticoids were found without associated increases in the excretion of pregnanediol (Figures 12 and 13). Similar results were found in two subjects who were given Compound F by mouth and in whom pregnanediol excretion was, if anything, depressed during the elevation of formaldehydogenic corticoids and the lowering of eosinophils (Figure 14).

It was of course anticipated that Compound F would give the same result as Compound E since there is both *in vivo* and *in vitro* evidence that the liver converts a portion of administered Compound E to Compound F (20, 54). Using paper chromatographic analysis of urine, we also have demonstrated the conversion both from E to F and from F to E in experiments in which the substances were separately administered to adrenalectomized patients (191).

It appears then that surgery and pituitary stimulation of the adrenal cortex cause the liberation of a substance or substances distinct from the well-recognized glycocorticoids. This is as much as can be concluded at the present time. That the precursors of pregnanediol are of the 11-desoxy or mineralocorticoid type is possible, but as yet unproved.

E. Desoxycorticosterone Administration and Alteration of the Na/K Ratio of the Diet

In what way are the findings with regard to the pregnanediol fraction of urine related to the original proposition which we started out to investigate: that is, the question of the production after surgery of hormones specifically concerned with salt retention?

In general it has been possible to confirm the findings of the previous workers regarding the conversion of desoxycorticosterone to pregnanediol. The findings have not been uniformly striking, however, nor entirely consistent. Figure 15 illustrates the pregnanediol in 6 male subjects in whom pregnanediol excretion following desoxycorticosterone administration was studied. In 4 out of the 6 cases the excretion of this metabolite was apparently increased over basal levels. It

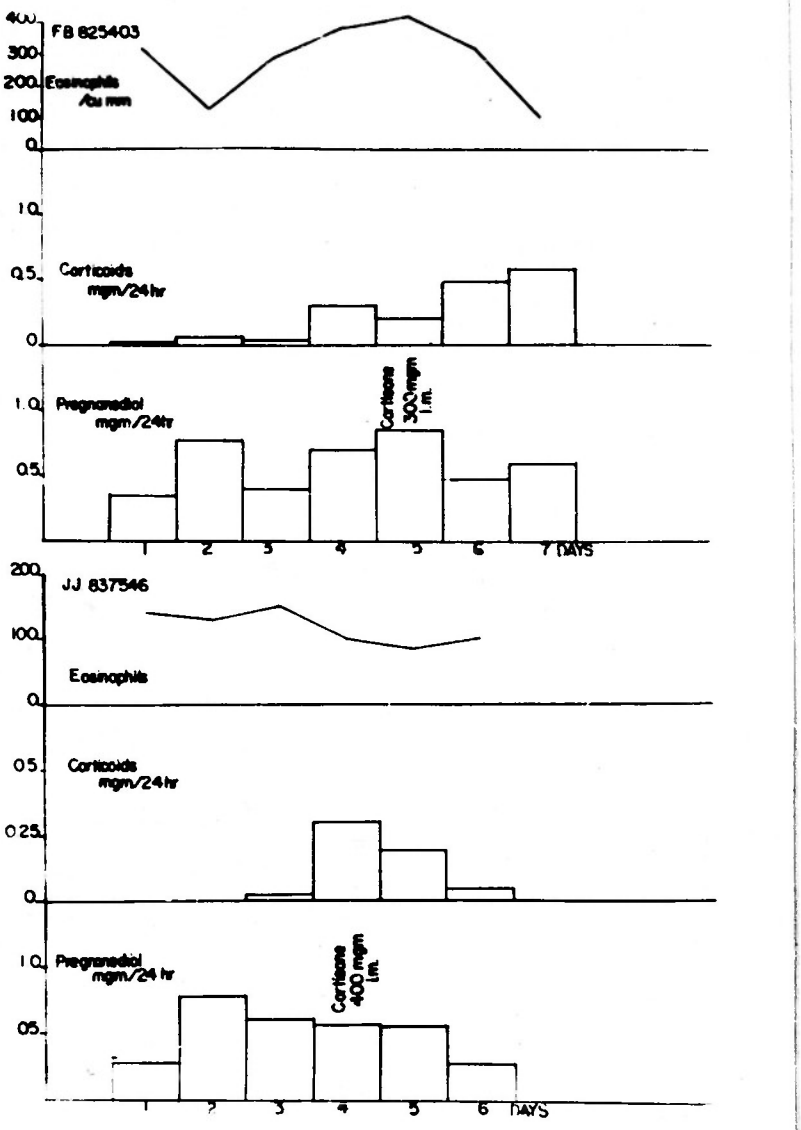


Figure 12. Excretion of pregnanediol and formaldehydogenic corticoids and eosinophil response during intramuscular administration of cortisone.

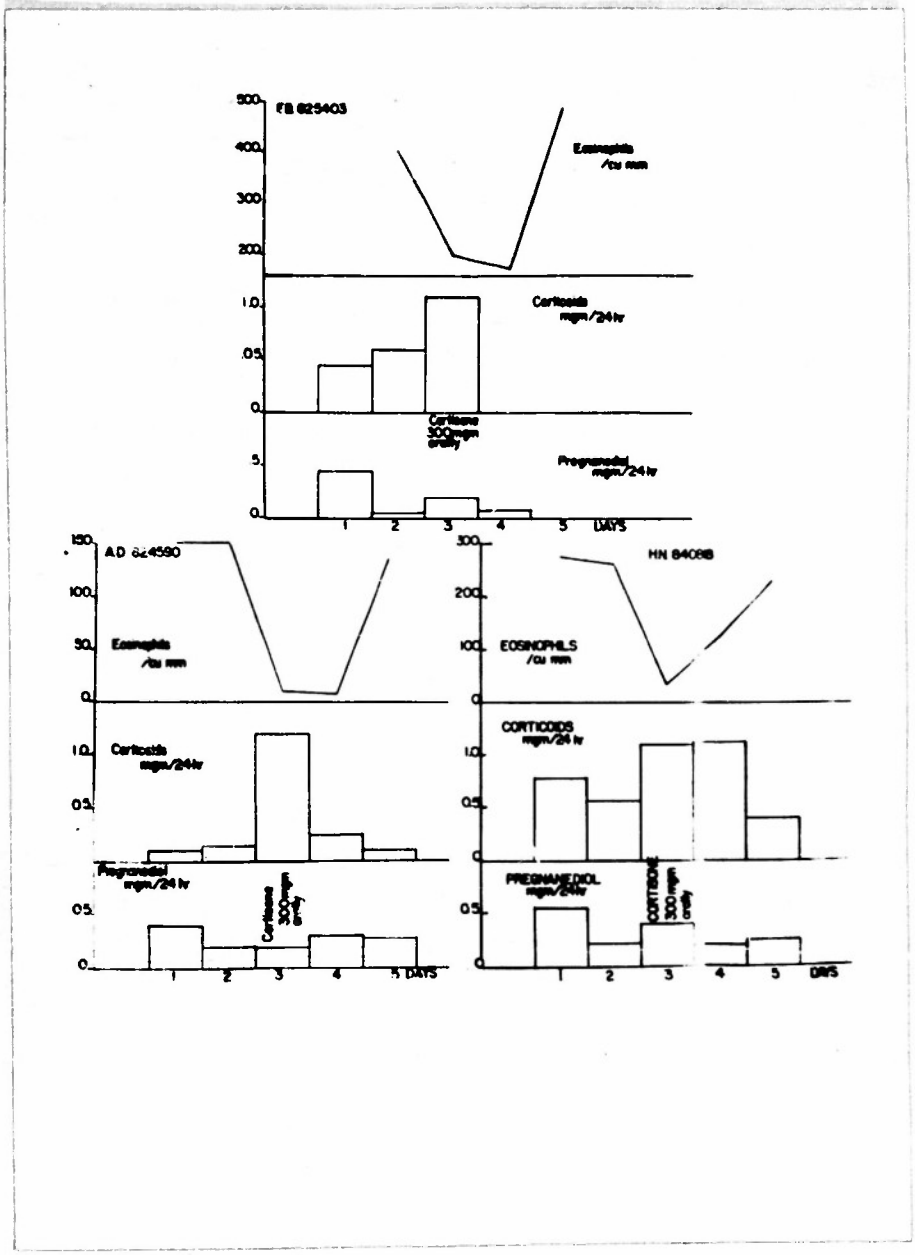


Figure 13. Eosinophil response and excretion of pregnanediol and formaldehydogenic corticoids in relationship to oral cortisone administration.

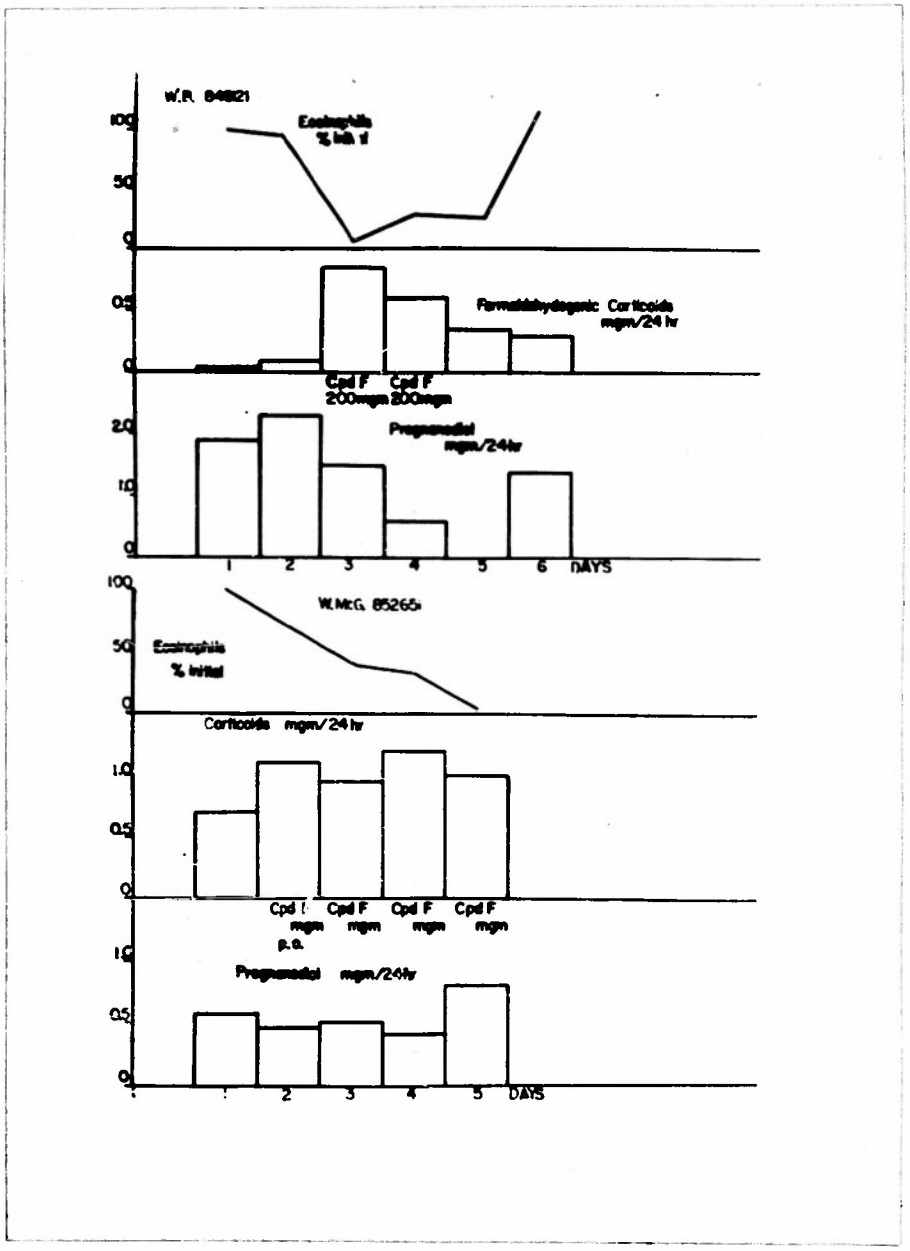


Figure 14. Response of eosinophils, formaldehydogenic corticoids and pregnanediol during oral administration of Compound F in 2 patients.

was not possible, however, to give desoxycorticosterone to humans in amounts at all comparable to the quantities of Compounds E and F which were employed in the experiments cited above. This may be responsible for the failure to find striking evidence of increased pregnanediol in these experiments. One might expect a more clear-cut effect in patients without adrenals and this was found to be true in 2 adrenalectomized patients shown in Figure 16. These patients were maintained on cortisone alone during the control period and desoxycorticosterone then was added without altering the cortisone dosage.

It would of course be of great interest to investigate pregnanediol in subjects on the low sodium, high potassium intake described in Section 3. Such experiments are in progress, but conclusive results have not yet been obtained.

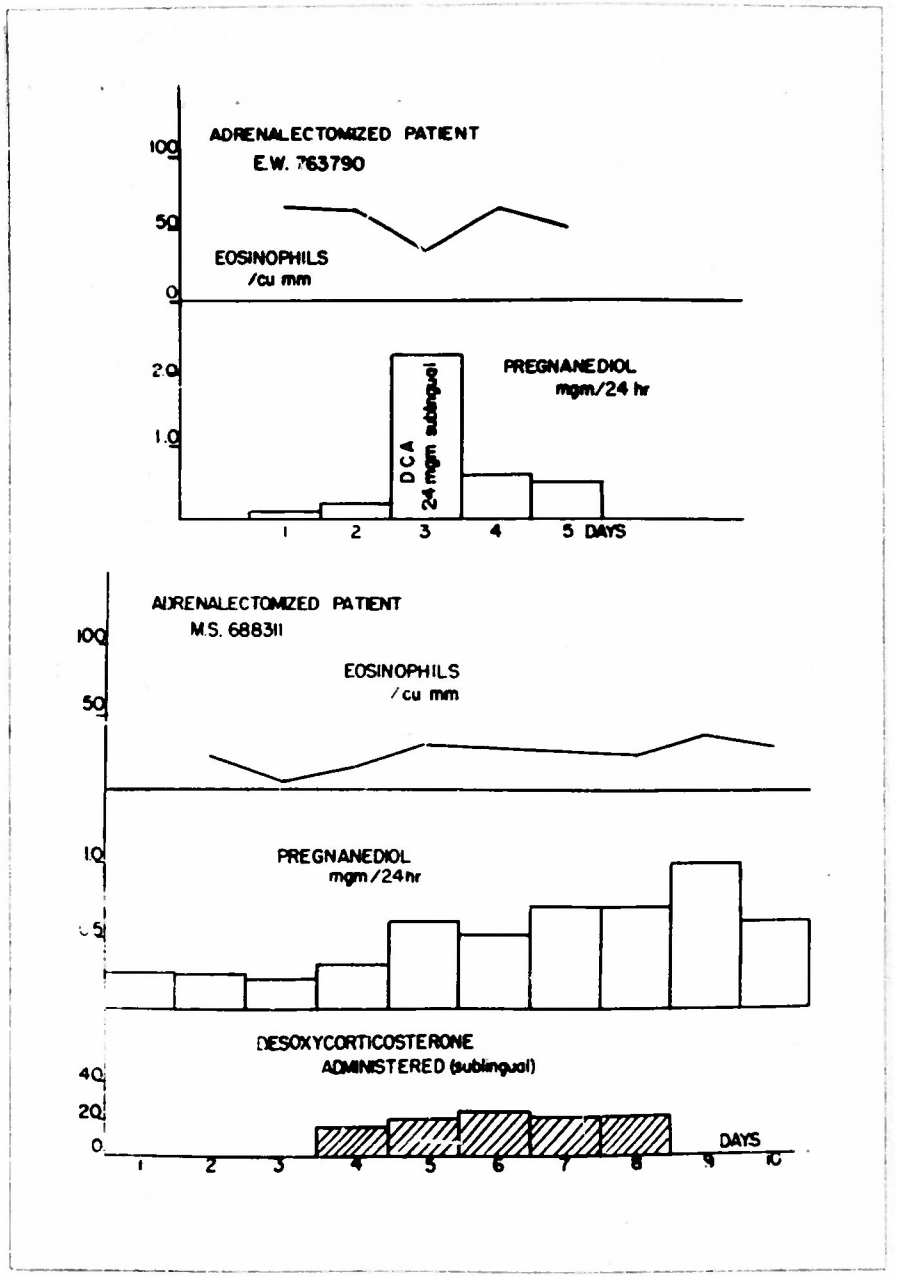


Figure 15. Pregnanediol excretion during intramuscular and sublingual administration of desoxycorticosterone acetate.

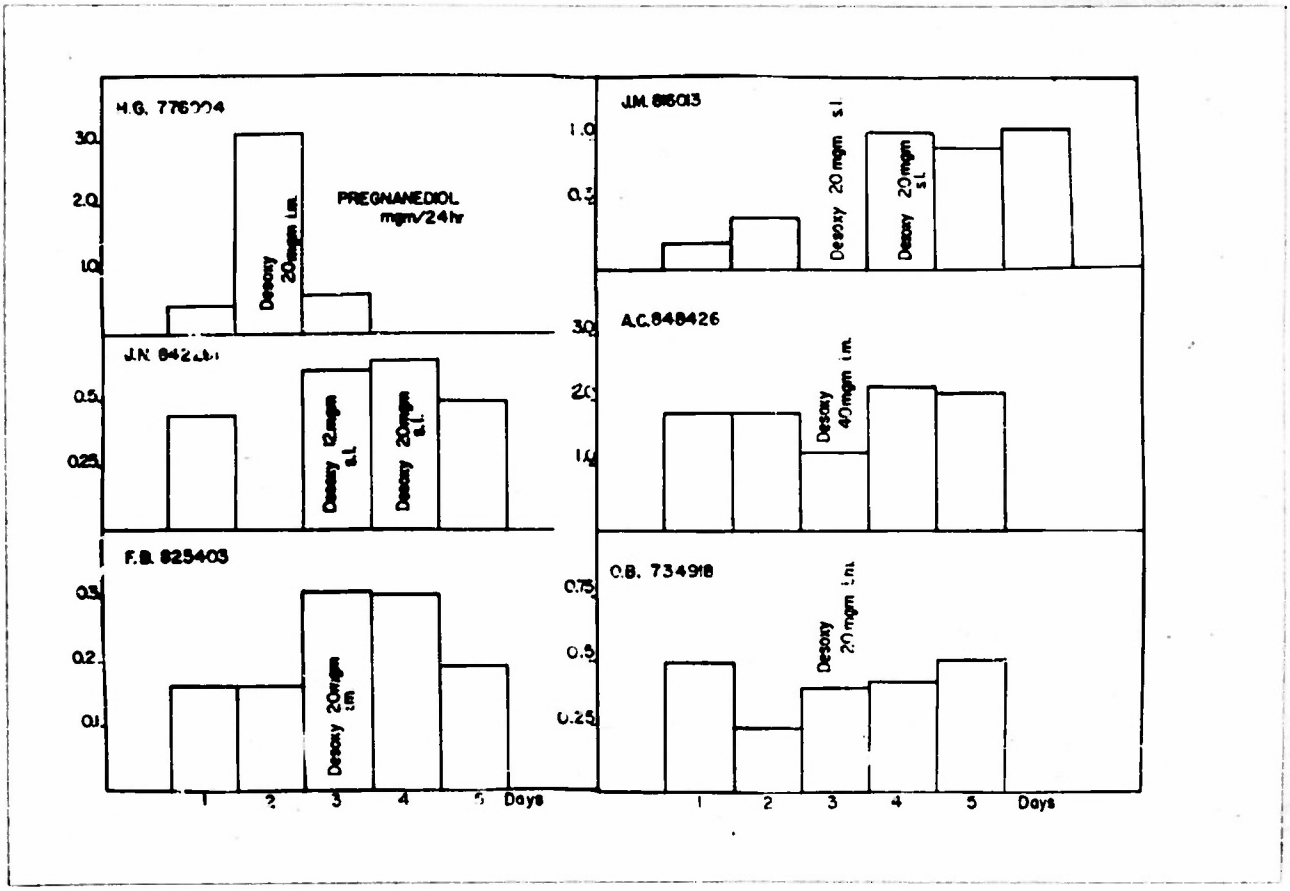


Figure 16. Relationship of pregnanediol excretion to administration of desoxycorticosterone acetate in 2 adrenalectomized patients.

INTERPRETATIONS

I. EXTRACELLULAR ELECTROLYTE CHANGES

It is apparent that the depression of sodium and chloride concentrations which occurs after surgery is a perfectly constant phenomenon which occurs immediately after surgery, lasts five to six days, and in general is chronologically related to the fall and subsequent rise of the eosinophil count. This reduction of electrolyte concentration is occasionally so severe as to result in serious symptoms which have been referred to as "water intoxication". The basic picture, however, in both the "normal" postoperative cases and the symptomatic ones is one of dilution of the major extracellular ions. The term "dilution" seems to be a good one since it does not distinguish between a decrease in solute and an increase in the volume of the solvent. Clinically the effects of dilution are the same regardless of its cause and experimentally it is not at present possible to distinguish between a shift of the solutes out of the extracellular space and a shift of water into the extracellular space. It is hard to avoid the conclusion that this dilute state of the plasma is causally related to the urinary restriction of sodium and chloride, since it is well recognized that in the normal individual the kidney protects the extracellular sodium and chloride levels by restricting their excretion. Moore has used the term "sodium paradox" in reference to the fact that the serum sodium levels are low despite the low urinary concentrations (124). We would rather think of the phenomenon in reverse order, the renal withholding of sodium being a perfectly normal reaction to the depressed plasma level.

If one accepts this course of events, it remains to explain why the extracellular ions undergo dilution. This is the heart of the problem and has so far largely eluded investigation. Since it is apparent that sodium and chloride are not lost from the body, only two possible explanations exist. Either the extracellular space enlarges or the major ions become redistributed so that they come to occupy a position inside the cell. Unfortunately, most methods which have been applied so far do not permit this distinction to be made. Certainly a tendency

to water retention as illustrated by the slow fall in body weight in our cases is part of the answer. Moyer has demonstrated this nicely in experiments which reveal the difference in response of normal and postoperative subjects with respect to response to water administration (126, 127). Following the intravenous administration of 5% glucose solution to normal individuals, diuresis is prompt and there occurs no dilution of the serum sodium levels. In postoperative patients, on the other hand, the diuretic response is slow and sodium levels fall strikingly.

The question of determining whether hyponatremia occurs from the movement of sodium outside the extracellular compartment or from an enlargement of the space itself depends on a measurement of the extracellular volume. Numerous such measurements have been made in postoperative patients, utilizing sodium thiocyanate as a tracer material (6, 58, 113, 119, 162, 163). Most of the studies have shown an enlarged thiocyanate space following surgery. The result of course varies considerably depending on the amount of parenteral fluid administered. Conclusions based on the use of thiocyanate, however, are not truly reliable under these circumstances. The thiocyanate ion behaves like chloride ion and hence only measures the "chloride space". If chloride were to move inside the cell one would expect that thiocyanate ion would behave similarly. The loss of thiocyanate from the extracellular compartment would give the impression of an enlarged extracellular volume though no change in the real volume change had occurred. Other techniques for extracellular volume determination would be desirable. Inulin space would be valuable, but the long period of infusion required for reaching equilibrium in the inulin space determination renders it impracticable in the rapidly-changing situation of the postoperative patient.

In an attempt to elucidate this problem we made use of a modification of the sodium thiosulfate space determination described by Cardoso and Edelman (21, 44). It was found that with a single injection and using the same blood samples, the thiocyanate and thiosulfate spaces could bedetermined simultaneously. By this

method it was hoped to take advantage of the fact that thiosulfate ion is apparently confined more rigidly to the anatomical extracellular space than is thiocyanate (68).

As had been previously reported, preoperative thiocyanate volumes were found to be consistently greater than those determined from thiosulfate distribution. (Average preoperative values: Thiocyanate: 24.8% body weight; thiosulfate: 20.4% body weight). Contrary to the findings of most groups, the average volumes did not increase, but decreased very slightly on the first day after surgery (differences of 1.4 and 1.3 per cent body weight), and returned to normal on the second postoperative day. In some individual instances the volumes increased and in others they decreased, but in all cases parallel changes occurred in the volumes as measured by the two methods. The usual drop in serum sodium and chloride values was seen so that total extracellular sodium as calculated from the thiosulfate space changed from 2.2 to 1.9 equivalents with an associated drop in chloride of from 1.6 to 1.3 equivalents. During this period the outputs of sodium and chloride were 48 and 75 milliequivalents respectively. This left unexplained deficits of 260 mEq. of sodium and 220 mEq. of chloride. This deficit cannot be accounted for without invoking a sequestration of sodium and chloride outside of the extracellular space. If, on the other hand, chloride moved into the cell why did not a greater discrepancy develop between the thiosulfate and thiocyanate values? We must admit that the mechanism of disappearance of sodium and chloride from the plasma in the postoperative patient remains a mystery, but whatever the mechanism, the phenomenon must be an important factor underlying the sharp restriction of salt output by the kidney.

In general, the period of eosinophil depression and electrolyte depression were about the same. This does not imply any causal relationship between adrenal function and electrolyte dilution, but more likely is only indicative of the fact that the same factors of operative stress were stimulating both electrolyte changes and pituitary-adrenal activity. It is of interest that the pattern of serum electrolyte changes corresponds exactly to the changes described by Selye during the "shock", "counter-shock" and "resistance" phases of the adaptation syndrome

except for the fact that a true hyperchloremic phase is not seen in the human (146), (Figure 1). This is further evidence that the changes are the result of non-specific stress and not merely artifacts produced by parenteral fluid therapy.

II. THE SIGNIFICANCE OF POTASSIUM LOSS

It has been mentioned earlier the loss of potassium from the cell results in sequestiation of sodium within the cell with a resultant extracellular alkalosis, chloride being lost in the urine as the extracellular bicarbonate increases. Darrow has postulated that 2 sodium ions and one hydrogen ion move into the cell for each 3 potassium ions lost, thus explaining the extracellular alkalosis associated with potassium deficiency (31). The findings here confirm previous studies showing that serum potassium was lowered during the postoperative course and it was of interest that a mild alkalosis was seen, the bicarbonate being maximal in the average case on the third postoperative day. It is unlikely, however, that the early depression of sodium occurring in our cases in the first 24 hours is a manifestation of the intracellular migration of sodium accompanying potassium depletion. Classical potassium deficiency is not characterized by low serum sodium levels. Alkalosis was not severe in these patients and was not maximal until the third day after operation, whereas the fall in serum sodium was immediate. Furthermore the development of potassium-deficiency-alkalosis picture involves an excessive loss of chloride in the urine. This is the antithesis of the actual finding in early postoperative patients.

III. ENDOCRINE FACTORS

Recent writers have all emphasized the importance of accelerated adrenal activity as the mechanism responsible for postoperative sodium and chloride retention, potassium loss and negative nitrogen balance (48, 75, 76, 77, 78, 123, 124). One wonders, however, whether this is the only factor involved and even whether it is a necessary factor. In this connection some experiments of Ingle are relevant (97). Ingle observed that if rats were subjected to fractures of the long boner, a characteristic pattern of positive sodium and chloride balance and

negative potassium and nitrogen equilibrium could be demonstrated. These phenomena were not seen in adrenalectomized rats. If, on the other hand, the adrenalectomized rats were maintained on a constant amount of adrenal extract, fractures would result in a metabolic picture identical with that seen in the intact rats despite the fact that no change in adrenal function or adrenal replacement occurred. In other words the presence of adrenal glands was necessary, but a changing level of adrenal function was not. There seems to be no good reason why the implications of these experiments might not apply to the human. Nor does there appear to be any reason for not believing that more than one mechanism may be operating to produce this metabolic picture.

IV. THE QUESTION OF SPECIFIC MINERALOCORTICOIDS

It is obvious that the experiments described here have not entirely answered the question of whether the adrenal glands under surgical stress release 11-desoxy-compounds or substances specifically concerned with electrolyte metabolism. Nevertheless from the observations which were made some limited conclusions can be drawn.

Since neither eosinopenia nor increase in formaldehydogenic corticoid excretion occurred following institution of a very rigid low sodium, high potassium regimen, it is clear that under anything approaching physiologic circumstances the pituitary corticotrophic mechanism is not involved in the response of the body to the necessity for sodium conservation.

It is still entirely possible, however, that stress and adrenal stimulation do cause the release of mineralocorticoids of the 11-desoxy type. It is clear from our findings with regard to pregnanediol excretion following surgery and during ACTH treatment that adrenal stimulation results in the secretion of some substances beside the well-known glycocorticoids (Compounds E and F). The only cortical substance at present known to be metabolized by this route is 11-desoxycorticosterone. Other steroids (e.g. Compound B) should be tried before one could safely state that and 11-desoxy substance is the precursor. The recent findings of Wolfson and Conn

have also demonstrated that adrenal stimulation results in the output of substances distinct from Compounds E and F (28, 186). In experiments quite analogous to ours, they found that the Pettenkofer chromagens were increased following ACTH therapy, but not following the administration of Compounds E and F. The effect of surgery was not investigated.

The knowledge obtained from studies of urinary excretion studies has in recent months been augmented considerably by the analysis of adrenal perfusates and adrenal vein blood. This work, pioneered by Pincus and his associates, is now being performed by a number of groups (83, 84, 141, 159, 160). From such analyses, it has been determined that the adrenal probably produces Compounds F and B as well as small amounts of desoxycorticosterone and Reichstein's Substance S. Factors which might be involved in an accelerated elaboration of the last two compounds have not been investigated.

Simpson, using a chromatographic method has separated a powerful salt-retaining substance from dog and monkey adrenal-vein blood, the chemical nature of which is unknown (153). Recent experiments with 2,2-bispara-dichlorophenyl-1,1-dichloroethane which selectively destroys the reticular and fascicular zones of the adrenal cortex have produced animals with normal electrolyte metabolism despite the obliteration of other adrenal moieties (18). Such findings argue for the independent, salt-regulating zona glomerulosa as suggested by Greep.

V. ADRENAL FUNCTION, ELECTROLYTE DILUTION AND WATER INTOXICATION

The foregoing studies have shown that the depression of extracellular sodium levels is an entirely constant finding after operations and that in uncomplicated instances this depression is maximal on the first or second postoperative day. The cases of postoperative water intoxication occurring most frequently between 24 and 48 hours after operation, were characterised by very low sodium values and hence

appeared to represent an exaggeration of what can be referred to as a normal postoperative reaction. To what extent is adrenal function implicated in either the normal or the exaggerated picture?

Selye has shown that chloride depression during the "shock phase" of the adaptation syndrome is more profound in adrenalectomized animals and that the return to normal which should occur in the "counter-shock phase" is largely impaired (147). Similarly it has been repeatedly demonstrated that adrenal insufficiency greatly increases the susceptibility of animals to water intoxication and that large amounts of adrenal hormones will render animals completely refractory to this disturbance (63, 64, 65, 81, 161). This relationship has been used by Woodbury as a method for assaying the action of certain types of adrenal hormones (187, 188, 189). This action was first shown to be effective in the human by McQuarrie and his associates (121, 144).

In the face of this evidence, it is a temptation to implicate a relative deficiency of adrenal function in those individuals who suffered the effects of water intoxication, and in particular those who did not receive unduly large amounts of water. Nevertheless only one of the patients showed an eosinophil count which was not within the range normally anticipated after operations. It should be emphasized, however, that the eosinophil count is a very sensitive test of adrenal function. It is probably too sensitive to be used for comparing degrees of hyperfunction which occur after operations in different individuals. It has been suggested that the 17-ketosteroids would be a better quantitative index of the adequacy of postoperative adrenal reaction (11). The postoperative serum sodium level is the resultant of poorly understood factors leading to hypotonicity on the one hand and the sodium retaining and diuretic effects of adrenal hormones on the other. For this reason we have come to feel that the sodium level on the first or second day after operation is a more valuable index of the effectiveness of the patient's response to the stress of operation than is the eosinophil count.

In this connection it is of interest that, whereas the eosinopenic response in the highly radical operations was practically identical with that associated with standard procedures, the depression of sodium and chloride was significantly greater in the former group.

VI. FUTURE INVESTIGATION: OTHER ENDOCRINE AND NON-ENDOCRINE INFLUENCES

The experiments reported here represent only a few of the approaches which can be utilized in an attempt to elucidate the background of electrolyte metabolism in surgical patients. Many problems await the development of adequate analytical methods. This applies to the study of the various fluid compartments. It is also the limiting factor in the advance of knowledge concerning the precise steroid hormones involved in the various manifestations which have been discussed here. In recent months we have been gaining experience with newer chromatographic methods which greatly facilitate the separation of individual steroids in blood and urine. At present we are applying such techniques to follow the metabolism of various steroids administered to adrenalectomized patients (15, 191). We are investigating the urinary steroids excreted in subjects on intakes characterized by various sodium/potassium ratios. These findings will eventually be applied to a detailed analysis of the blood and urine of postoperative patients.

Some other factors which may relate the effects of surgery to water and salt metabolism are worthy of serious consideration. Hayes and associates have, on the basis of indirect evidence, recently suggested that an excess production of posterior pituitary antidiuretic hormones plays a role in the water retention associated with anesthesia and surgery (82). This is a very reasonable hypothesis, but further proof must await more specific methods for the measurement of ADH than the bioassay procedures which are now available.

A circulatory mechanism may also be of great importance in the genesis of postoperative salt retention. It is recognized that the renal management of sodium ion is very delicately related to changes in the cardiac output, decreases in cardiac output being compensated for by reduction of sodium excretion (16). Using a

ballisto-cardiographic method we have obtained evidence which suggests that the cardiac output is quite severely reduced by anesthesia and surgery even in instances where hemorrhage and shock are not involved (192). This is another facet of the problem to which more precise methods of measurement should be applied.

CONCLUSIONS

The postoperative metabolic picture is characterized by an abnormally dilute status of the major extracellular electrolytes and by retention of sodium and chloride from the urine. Concomitantly, retention of water can be demonstrated by comparison of the body weight changes after operation with those of non-operated individuals under similar conditions of nourishment. It is clear moreover from the two groups of patients studied here that the phenomena of dilution are in greater evidence in patients undergoing prolonged extensive surgery than in those who have had more standardized procedures. Both endocrine and non-endocrine factors undoubtedly contribute to this picture.

Since the depression of serum sodium and chloride levels following surgery is an entirely consistent finding, seen in all types of surgical patients, it is reasonable that this itself partly accounts for the reported retention of sodium and chloride from the urine.

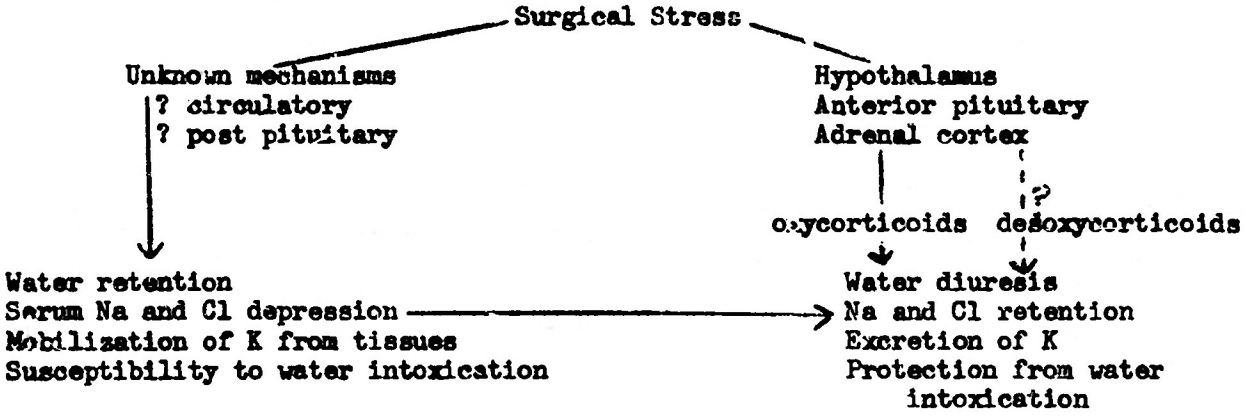
It has been generally accepted that pituitary mobilization of salt-retaining adrenal hormones is responsible for postoperative positive balance of sodium and chloride. In this connection there can be no doubt that large amounts of adrenal hormones are mobilized after operations. In addition to the evidence consisting of eosinopenia and glycocorticoid production which are well recognized, we have demonstrated the presence of another hormone metabolite or group of metabolites (pregnanediol) which apparently has different precursors from those which give rise to the urinary glycocorticoids.

Nevertheless, despite the fact that desoxycorticosterone is the only corticoid we now know which is metabolized to pregnanediol, the proof that surgery or pituitary corticotrophic stimulation produces desoxycorticoids or any hormones whose specific activity is one of salt regulation remains incomplete. Some negative evidence on this point exists in our finding that the strongest "salt stress" we could impose on the adrenals of human subjects evoked no evidence of pituitary

corticotrophic activity. This is in harmony with the work of Greep who found mineralocorticoids in the rat to be independent of the pituitary.

Whether or not specific salt-regulating corticoids are involved there seems to be little doubt that adrenal hormones play a role in the postoperative regulation of fluid and electrolyte balance. The glycocorticoids, though usually thought of as regulators of organic metabolism have definite effects on mineral balance and profoundly influence the excretion and distribution of water.

It would appear then that surgical stress influences the metabolism of water and electrolytes through at least two channels. Through mechanisms about which almost nothing is known, water retention and depression of sodium and chloride concentrations take place. These occurrences are deleterious. Simultaneously, however, the pituitary-adrenal axis is stimulated with the release of hormones capable of minimizing these effects by causing sodium retention and water diuresis. The situation at any point in time represents the resultant of these antagnostic effects of stress. The following diagram illustrates such a scheme.



It is apparent that the factors in the left hand column dominate the picture in the earliest part of the reaction to surgery. This corresponds to the "shock phase" of Selye's adaptation syndrome. Subsequently the actions which are mediated by the pituitary-adrenal system take over to counteract and minimize these deleterious

effects. The course of events can be mapped by the course of the serum sodium. We feel, therefore, that if any one criterion were to be chosen, the serum sodium would constitute the best index of the effectiveness with which the patient has responded to the harmful effects of surgical insult.

SUMMARY

(1) From a study of 40 patients following standard uncomplicated major surgical procedures a consistent pattern of changes in fluid and electrolyte distribution and adrenal activity could be described. Eosinophils reached a minimum level in 24 hours and returned to normal in 4 to 6 days. Blood sodium and chloride concentrations fell immediately following surgery and returned to preoperative values over approximately the same period of time as the eosinophils. Sodium levels responded toward normal somewhat more rapidly than did the chlorides. Accompanying these changes, there was a very slight tendency to alkalosis which was maximal in the average instance on the third postoperative day. Potassium levels of the serum were depressed throughout the postoperative course.

A tendency to the retention of body water was manifested by a failure of the body weight to fall as rapidly as would be expected in non-operated subjects on similar conditions of inadequate nutrition.

(2) In 16 patients who underwent unusually long, extensive and complicated operations for cancer, it could not be demonstrated that the eosinophil response differed from that in the standard operations provided that no postoperative complications occurred. The changes in fluid and electrolyte metabolism, on the contrary, were quantitatively different. Serum sodium and chloride levels dropped lower and returned to normal more slowly. This was accompanied by evidence of a greater tendency to the retention of water.

(3) In 20 patients serious central nervous system manifestations could be related to an exaggeration of the ordinarily dilute state of the postoperative electrolytes. These instances of so-called "water intoxication" took the form of seizures or coma occurring most frequently between the first 24 and 48 hours after surgery at the time when the serum electrolytes are normally expected to

be most depressed. The only constant finding in these instances was extremely low serum sodium and chloride values. Evidences of positive water balance was present in most instances and overdosage of parenteral fluid was responsible for 6 cases.

Despite the wealth of experimental evidence linking adrenal function with susceptibility to water intoxication, it was not possible to demonstrate by eosinophil counts and eosinopenia tests any adrenal deficiency in this group except in the instance of one patient whose eosinophil response to surgery was clearly abnormal.

(4) Experiments were devised to further elucidate some aspects of the role of the pituitary-adrenal axis in the control of sodium and chloride balance in the postoperative patient. The first of these was an attempt to determine whether adrenal mineral-regulating corticoids were under the control of the anterior pituitary. In 11 subjects, the imposition of a severe "salt stress" in the form of a low sodium high potassium diet produced no evidence for pituitary corticotrophic activity as measured by eosinophils and formaldehydogenic corticoid excretion. This was in harmony with rat experiments reported by others which have suggested that mineral-regulating corticoids are independent of the pituitary.

(5) Because previous workers had demonstrated that the mineralocorticoid 11-desoxycorticosterone could be metabolized to pregnanediol an attempt was made to find the latter substance in the urine of postoperative patients. In 7 male patients studied, material in the so-called "pregnanediol fraction" was found to be elevated in all instances for the first 2-3 days after operation. ACTH produced similar results but the administration of Compounds E and F did not. The lowest urinary pregnanediol excretions measured were in 3 gonadectomized adrenalectomized individuals. The conclusion seemed justified that the precursors of this material in the urine of postoperative males are one or more adrenal steroids

distinct from the glycocorticoid Compounds E and F. That they are 11-desoxy compounds remains to be proved or disproved.

(6) It was concluded from these studies and those of others that both endocrine and non-endocrine factors are important in the disturbance of electrolyte metabolism which is characteristic of the postoperative state. The well-known retention of salt by the kidney must be partly due to the relatively dilute state of the major extracellular constituents. In addition, an excessive production of adrenal hormones as a result of stress and pituitary-adrenal activity undoubtedly plays a role, but whether this activity represents the presence of so-called mineralocorticoids or is merely an incidental action of glycocorticoids is not clear. Evidence on both sides of this question has been presented. Further investigation should be directed toward the development and utilization of better techniques for properly describing the nature of extracellular ion dilution which occurs after surgery and for accurately identifying individual endocrine substances.

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